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IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF NEW JERSEY

DEPOMED, INC. and GRUNENTHAL : Civil No.
GMBH, : 13-cv-4507-CCC
 :
Plaintiffs/Counterclaim : TRANSCRIPT OF
Defendants, : TRIAL PROCEEDINGS

v. :

ACTAVIS ELIZABETH LLC and :
ALKEM LABORATORIES LIMITED,

:
Defendants/Counterclaim :
Plaintiffs. :

-----x

: Civ. No. 13-cv-7803-CCC
AND CONSOLIDATED CASES : Civ. No. 13-cv-6929-CCC
 : Civ. No. 14-cv-3941-CCC
 : Civ. No. 14-cv-4617-CCC
 : Civ. No. 14-cv-6797-CCC
-----x

Newark, New Jersey
March 16, 2016

BEFORE:

THE HON. CLAIRE C. CECCHI, U.S.D.J.

Reported by:
CHARLES P. McGUIRE, C.C.R.
Official Court Reporter

Pursuant to Section 753, Title 28, United States
Code, the following transcript is certified to be
an accurate record as taken stenographically in
the above entitled proceedings.

s/CHARLES P. McGUIRE, C.C.R.

CHARLES P. McGUIRE, C.C.R.

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1 THE COURT CLERK: All rise.

2 THE COURT: Good morning, everyone. Have a seat.

3 Everyone is well? Good. We have an extra half
4 hour today.

5 (Laughter)

6 THE COURT: Hope that did everyone well.

7 All right. Let's see. Let's get everyone onto
8 the record, and we'll begin. Let's start with the
9 Plaintiffs.

10 MR. MILLER: Good morning, Your Honor.

11 Keith Miller from the firm of Robinson Miller,
12 Newark, New Jersey, on behalf of the Plaintiff Depomed.

13 With me are my co-counsel from the Gibson Dunn
14 firm, Christine Ranney, David Glandorf, and Timothy Best.

15 THE COURT: Thank you.

16 MS. CHUDEREWICZ: Good morning, Your Honor.

17 Melissa Chuderewicz from Pepper Hamilton on behalf
18 of Plaintiff Grunenthal, and with me are my co-counsel from
19 the Finnegan law firm, Bill Lewris, Linda Wadler, and
20 Christie McIntyre.

21 THE COURT: Thank you. Good morning.

22 MS. WIGGINS: Good morning, Your Honor.

23 On behalf of the Actavis Defendants, I'm
24 Sheila Wiggins from Duane Morris, and with me are my
25 colleagues, Patrick Gallagher and Anthony Fitzpatrick.

1 THE COURT: Thank you. Good morning.

2 MS. HANDLER: Good morning, Your Honor.

3 Amy Handler from Sills Cummis & Gross on behalf of
4 Defendant Roxane Labs, and with me are my co-counsel from
5 Latham & Watkins, Terrence Connolly, Lauren Sharkey, and
6 Ken Schuler will be back later.

7 THE COURT: Okay. Thank you.

8 MR. RICHTER: Good morning, Your Honor.

9 James Richter, Winston & Strawn, on behalf of
10 Alkem, and I'm going to allow my co-counsel to introduce
11 themselves.

12 MR. RIAZ: Good morning, Your Honor.

13 Ahmed Riaz from Schiff Hardin on behalf of
14 Defendant Alkem.

15 MR. ALY: Good morning. Imron Aly.

16 THE COURT: Good morning.

17 MR. HARP: Good morning, Your Honor. Jason Harp.

18 THE COURT: Good morning.

19 All right. So are we going to be doing some
20 continuation of Dr. Steed, of the direct, or not?

21 MR. HARP: No further direct.

22 THE COURT: I know we talked about potentially
23 there being 10 more minutes.

24 MR. HARP: Thank you for the opportunity, Your
25 Honor. No further direct.

1 THE COURT: All right, fine. Let's begin with the
2 cross, then.

3 If we may have the witness return to the witness
4 stand.

5 J O N A T H A N S T E E D, called as a witness on behalf
6 of the Defendants, and having been previously sworn,
7 testified as follows:

8 THE COURT: And again, sir, I will remind you that
9 you are under oath.

10 Good morning. How are you?

11 THE WITNESS: Good morning. I'm fine, thank you,
12 Your Honor.

13 THE COURT: Good.

14 MS. RANNEY: And we have some binders.

15 THE COURT: You may begin.

16 Did you get a chance to look at the exhibits?

17 MR. HARP: Yes, Your Honor.

18 One issue with PTX 297, which appears to be a
19 European patent document. I don't believe Mr. Steed has
20 ever testified about that, nor is it in his report, so I'm
21 just raising that as an issue so that a foundation may be
22 laid.

23 THE COURT: Okay. Anything else?

24 MR. HARP: No, Your Honor.

25 THE COURT: Anything with the demonstrative?

1 MR. ALY: Just a moment?

2 THE COURT: It looks like there is only one
3 demonstrative? Or no, two.

4 MS. RANNEY: Just a couple.

5 MR. HARP: No issues, Your Honor. Thank you.

6 THE COURT: Also, I just want to remind everyone
7 to speak into the mike as well, myself included.

8 Any issue with respect to the demonstrative?

9 MR. HARP: No, Your Honor. Thank you.

10 THE COURT: Thank you. Or demonstratives, plural.

11 Thank you. Let's begin.

12 CROSS-EXAMINATION

13 BY MS. RANNEY:

14 Q. Good morning, Dr. Steed.

15 A. Good morning, Ms. Ranney.

16 Q. I just wanted to confirm a couple of things to start.

17 Now, you testified yesterday regarding
18 reproductions of Example 25 conducted by Marita Mueller;
19 correct?

20 A. Yes.

21 Q. Let's talk about the first of those three
22 reproductions, which was Sample GB-Bu322-1-1. Is it okay if
23 I refer to that sample as 1-1?

24 A. Okay.

25 Q. Now you reviewed the XRPD pattern for sample 1-1,

1 didn't you?

2 A. Yes.

3 Q. And you did not conclude that Form A was present in
4 that XRPD pattern, did you?

5 A. I did not.

6 Q. Moving on to the third of her reproductions that
7 resulted in Sample GB-Bu322-1-3.

8 And I'll refer to that one as 1-3.

9 A. Okay.

10 Q. Did you review the XRPD pattern for Sample 1-3?

11 A. I did.

12 Q. And you did not conclude that Form A was present in
13 that pattern, did you?

14 A. I didn't, but it was very noisy.

15 Q. But despite the fact that it was noisier than say the
16 pattern for 1-1, you did not conclude that there was any
17 Form A in there.

18 A. I didn't.

19 Q. All right. Now, you would agree that there are
20 samples of Form B of tapentadol hydrochloride that exist at
21 room temperature; right?

22 A. Impure samples, yes.

23 Q. Yes. And you testified, for example, yesterday, about
24 batch zero; correct?

25 A. Yes.

1 Q. And you know that batch zero was synthesized in 1994.

2 A. I believe that's correct.

3 Q. Okay. And your counsel put up the XRPD pattern for
4 batch zero; right?

5 A. Yes.

6 Q. And you agree that batch zero was Form B; you did not
7 conclude there was Form A in that pattern, did you?

8 A. No, I didn't. Again, it's somewhat noisy, but I
9 didn't see any Form A.

10 Q. And the XRPD pattern for batch zero was measured at
11 the end of 2001?

12 A. I believe so.

13 Q. Okay. So batch zero remained Form B for almost eight
14 years.

15 A. Certainly when it was measured, it seemed to be Form
16 B.

17 Q. Okay. But you took the position yesterday that batch
18 zero and other samples of Form B that were stable at room
19 temperature contained impurities; correct?

20 A. Yes.

21 Q. And those impurities allowed Form B to be stable at
22 room temperature?

23 A. That's right.

24 Q. Now, is there any particular impurity or impurities
25 that you think stabilized Form B, or is it just impurities

1 in general?

2 A. I think it must be some particular impurities, but I
3 don't know which specific ones.

4 Q. Okay. A particular impurity or impurities.

5 A. Yes.

6 Q. Is it okay if I refer to that as the key impurity?
7 Because I think we're going to be talking about it a lot.

8 A. If you wish.

9 Q. Okay. Thank you.

10 So given that you don't know the identity of this
11 impurity or impurities, I assume you haven't seen any
12 empirical data on their effects on polymorphic form?

13 A. I believe the DSC and x ray data referred to yesterday
14 are empirical data.

15 Q. I'm sorry, Doctor. I was talking about empirical data
16 on the effect of the key impurities specifically on
17 polymorphic form.

18 A. Well, the effect seems to be to retard the rate of
19 transformation from B to A, so with regard to that effect,
20 the DSC and x ray data are empirical data.

21 Q. Okay. And you testified yesterday regarding a few
22 Grunenthal documents that listed various samples and their
23 impurity levels; correct?

24 A. Yes.

25 Q. Okay. And you pointed out that the Form B samples in

1 these documents seemed to have higher levels of impurities
2 than their Form A counterparts.

3 A. Yes, three particular impurities, if I'm thinking of
4 the ones you're thinking of.

5 Q. Okay. Yes. And that was your explanation as to why
6 we could have these samples of Form B; right?

7 A. I believe these samples of Form B are impure, and
8 those Form B samples had high levels of those three
9 particular impurities.

10 Q. Let's look at another Grunenthal document showing
11 impurity levels for different samples.

12 MS. RANNEY: If you can put up Plaintiff's Exhibit
13 507, and next to it the translation, which is Plaintiff's
14 Exhibit 1579.

15 Q. Have you seen this table before, Doctor?

16 A. I'm afraid I don't remember. I may have done, but I
17 don't remember.

18 Q. You reviewed Dr. Bernstein's report in connection with
19 this litigation; right?

20 A. Yes, I did.

21 Q. And did you review the documents cited in his report?

22 A. Yes, I did, mostly, yes.

23 Q. I understand there were a lot.

24 A. There was a lot.

25 Q. This was one of the documents cited in Dr. Bernstein's

1 report.

2 A. Okay.

3 Q. So you see a number of samples listed on the left-hand
4 column; right?

5 A. Yes.

6 Q. And at the bottom, we see two samples that you
7 testified yesterday, CEP1a and CEP2a.

8 A. Correct.

9 Q. You understand that these samples in the left-hand
10 column are samples of tapentadol hydrochloride; right?

11 A. It would seem so.

12 Q. And then in the far right-hand column, we have
13 impurities, and you recognize that BN300 and Bu351 are two
14 types of impurities; right?

15 A. Yes, they're two particular impurities.

16 Q. Okay. Let's look at the first sample on this table.
17 It's CEWS141/1.

18 A. Okay.

19 Q. Could you read for the record the percentages of
20 impurities listed for this sample?

21 A. Yes. It's BN300, 0.35 percent; Bu351, 0.2 percent.

22 Q. Okay. And this sample is listed as Form B; right?

23 A. That's what it says.

24 Q. So this is a relatively low level of impurities;
25 correct?

1 A. Well, of these two particular impurities, yes, they
2 are relatively low.

3 Q. Okay. You've reviewed the other levels of impurities
4 in this document?

5 A. I don't recall reviewing it, but I would have done if
6 it was in Dr. Bernstein's report.

7 Q. And, for example, if you go to the second page, and
8 look at one of the Form A samples, and it's CEHS93-95.

9 A. I'm sorry, just give me a moment. I was on the German
10 version. I'm just going to flip to the English version on
11 my page.

12 Q. Sure.

13 A. My German is nonexistent, I'm afraid.

14 Q. Same for me. So CEHS93-95.

15 A. And this is the second page?

16 Q. Yes. Sort of in the middle.

17 A. Okay.

18 Q. Could you read for the record the impurities listed
19 for that sample?

20 A. Yes. That's BN300, 1.15 percent; and Bu351, 0.35
21 percent.

22 Q. And those are both higher percentages than the
23 percentages for Form B we just looked at; right?

24 A. I'll have to check again.

25 Q. Sure.

1 A. Yes, we have .35 and .2 for 300 and 351, and now we
2 have 1.15 and .35 for this one, so, yes, they're higher.

3 Q. Thank you, Doctor.

4 You also testified yesterday regarding experiments
5 that were conducted at Crystallics, investigating the effect
6 of impurities on polymorphic form; right?

7 A. Yes.

8 MS. RANNEY: All right. Let's put up that report.
9 It's Defendants' Exhibit 995.

10 Q. And you recognize this as the report from Crystallics
11 that you testified about yesterday; right?

12 A. Yes.

13 Q. What's the date on this report? It's in the top right
14 corner.

15 A. May 2003.

16 Q. And could you read the first sentence of the third
17 paragraph that begins "An accelerated?"

18 A. "An accelerated experimental program (97 experiments)
19 has been performed at Crystallics BV."

20 Q. Okay. Let's go to page number 20952.

21 A. Sorry. I sort of have to find it. I thought it was
22 going to come up on the screen.

23 Q. It will.

24 A. Okay.

25 (The document was displayed.)

1 Q. I'll give you a moment.

2 A. Thank you.

3 I'm sorry, could you repeat the page number,
4 please?

5 Q. It's 20952 is the Bates number.

6 A. Okay.

7 Q. Okay. Could you read the heading at the top of this
8 page?

9 A. "Step 3-effect of impurities."

10 Q. And you testified about this page yesterday; right?

11 A. Yes.

12 Q. And looking at this page yesterday, you testified that
13 Crystallics concluded that impurities affected polymorphic
14 form, right, or at least these particular impurities?

15 A. I believe I testified that one of these particular
16 impurities had more of an effect on the formation of B than
17 the other one did.

18 Q. Okay, and why did you testify about that?

19 A. That's what it says here.

20 Q. Okay. And was your point to show that impurities
21 affects polymorphic form?

22 A. My point was that Crystallics believed that one of
23 these two particular impurities had an influence on
24 polymorphic form.

25 Q. Okay. If you look at Table 6.

1 A. Okay.

2 Q. And Table 6 is titled "Significant factors for the
3 responses in the Step 3 DoE," and we saw at the top of the
4 page that step three is effect of impurities; right?

5 A. Okay.

6 Q. And then let's look at the line for polymorph,
7 starting with impurity GRT4045Y.

8 The value there is zero; right?

9 A. That's what it says.

10 I must admit I'm not an expert in design
11 experiments methodology. It's a rather complex technology.

12 Q. You understand that this zero indicates that there was
13 no significant effect of this impurity on polymorphic form;
14 right?

15 A. I'm afraid I don't really understand what the notation
16 is in DoE. It's a complex system of methodology that we
17 don't do in my lab.

18 Q. Okay. The title of the table is "Significant factors
19 for step 3 DoE"; correct?

20 A. Indeed.

21 Q. And the zero would seem to indicate that they did not
22 find GRT4045Y to be a significant factor; correct?

23 A. I don't know that from my experience. All I can go is
24 by the legend of the table, which talks about what pluses
25 and minus means. It doesn't specify what the zero means.

1 What you say doesn't sound unreasonable, but I don't know
2 that from my experience.

3 Q. And looking at GRT0912Y, the value there is also zero;
4 right?

5 A. That's what it says.

6 Q. Okay.

7 MS. RANNEY: Can we move the magnifier down just a
8 little bit to get the last line?

9 Q. Could you read that last line there with the little
10 star?

11 A. "Factor interaction AC is also significant."

12 Q. Okay. Could you read the -- the last line of the
13 table is GRT 0912Y; is that right?

14 A. Yes.

15 Q. And then the value listed for GRT 4045Y is zero;
16 correct?

17 A. That's what it says.

18 Q. So that would indicate that GRT0912Y is also not a
19 significant factor when it comes to the other impurity;
20 correct?

21 A. I'm not quite sure what you mean by significant factor
22 when it comes to the other impurity.

23 Q. Doesn't this last line of the table indicate that zero
24 means not significant?

25 A. Yes, but I don't quite understand what the zero means

1 in terms of one impurity interacting with the other
2 impurity. The heading of the second column is the name of
3 one impurity, and the line you're pointing to is another
4 impurity, so that seems to be the influence upon one
5 another. But as I said, I'm not an expert in design of
6 experiments.

7 Q. Fair enough. Sorry. Actually, what I was hoping you
8 would look at or what I should have had you look at is the
9 note at the end of the table that says zero is not
10 significant.

11 A. Yes, that's what it says.

12 Q. Okay. So that would indicate to you that these
13 impurities 4045Y and 0912Y were not significant in terms of
14 polymorphic form; correct?

15 A. I can't conclude that because I don't really
16 understand the statistics of the design of experiments
17 methodology, but I can say that it does say zero, which says
18 not significant.

19 Q. Okay. Thank you.

20 MS. RANNEY: Could we look at Plaintiff's Exhibit
21 553?

22 Q. Could you read the title and the date of this
23 presentation for the record, please?

24 A. Yes. "CG5503 - Results of the crystallization
25 optimization at Crystallics, 2003-05-12."

1 Q. Okay and that would be May of 2003; correct?

2 A. I believe so, yes. It's in the British.

3 Q. Let's look at the second page of the document.

4 Could you just read the first bullet point for the
5 record?

6 A. "The project concerns a crystallization process
7 optimization study of CG5503 in which 97 crystallizations
8 were carried out by varying concentrations and solvents
9 (including mixtures) cooling rates, end temperatures and
10 seeding amounts."

11 Q. This would be the same May 2003 Crystallics study that
12 we were just talking about; right?

13 A. I believe so.

14 Q. Okay. Let's go to page 23 of the document. It's
15 Bates number 74898.

16 Could you read the title of the slide for the
17 record?

18 A. "The effect of impurities on the crystallization."

19 Q. And would you also read the first bullet point please?

20 A. Yes. "High levels of impurities GRT4045Y and GRT0912Y
21 were observed to have no effect on the polymorphic form
22 outcome in step 3."

23 Q. Okay. Let's get back to your opinion about the
24 impurities and their effect on polymorphic form.

25 It's your opinion that if you synthesized

1 tapentadol, say as in Example 25, and you do it cleanly, you
2 will always obtain some Form A; right?

3 A. Repeated correctly, you will get some Form A.

4 MS. RANNEY: Okay. Could we put up Defendants'
5 Exhibit 752? And let's go to Example 25 in Column 20.

6 Q. The goal of Example 25 is to produce compound (-21),
7 which is tapentadol hydrochloride; is that right?

8 A. Yes, (-21).

9 Q. And it says here that enantiomer (-21) was obtained in
10 45 percent yield; is that right?

11 A. Yes.

12 Q. Now this yield indicates that Example 25 is not a
13 particularly clean synthesis, doesn't it?

14 A. Yes, that's right. It's quite a low yield.

15 Q. So the Example 25 synthesis will generate some
16 impurities; right?

17 A. Not necessarily. It will generate some side product
18 or by-product, and that's what the zero means, that not all
19 the starting material has ended up to product.

20 Q. And the side product or by-products, could these be
21 impurities that stabilize Form B?

22 A. They could do if they're in the final sample. If
23 they're separated out during the process, then of course,
24 they won't be impurities, they would be separated out by
25 purification.

1 Q. But it is possible that the reproduction of Example 25
2 could generate either impurities or side products or
3 by-products that could stabilize Form B; right?

4 A. What do you mean by the reproduction?

5 Q. If one were to synthesize tapentadol hydrochloride
6 according to Example 25, one might generate impurities or
7 side products or by-products that could stabilize Form B; is
8 that right?

9 A. I don't think I can agree with that. Good chemical
10 practice means that you do purify your compound as best
11 you're able, and we talked about how purification is done
12 and how it's accessed. So a good chemist would try and get
13 a pure product.

14 Q. But a good chemist will never be able to get a
15 100-percent pure product; right?

16 A. No, that's true.

17 Q. There will always be some impurities that remain.

18 A. Yes, and there are particular criteria of purity that
19 chemists use.

20 Q. And in fact, you testified about the University of
21 Wisconsin reproduction or purported reproduction of Example
22 25; right?

23 A. Yes.

24 Q. And there were some impurities there as well.

25 A. Yes, there were.

1 Q. So isn't it possible that you could have a faithful
2 reproduction that generated enough of these impurities to
3 make it result in only Form B?

4 A. When you say "these impurities," are you referring to
5 the specific impurities that stabilize Form B?

6 Q. Yes.

7 A. I'm sorry, could you just repeat the question again?

8 Q. Sure.

9 Isn't it possible that a faithful reproduction of
10 Example 25 of the '733 patent would generate enough of the
11 key impurity to make the result only Form B?

12 A. No, I don't believe so.

13 Q. And why is that? What level of purity would you
14 require for a synthesis of tapentadol hydrochloride to be a
15 faithful reproduction of Example 25?

16 A. Well, we don't know what this impurity is that does
17 the stabilizing, so I can't really say what level of purity
18 would be. But we do have the evidence from Wisconsin's
19 reproduction that they did carry it out faithfully and they
20 did get Form A.

21 Q. So the University of Wisconsin has some impurities,
22 and your opinion is that that is a faithful reproduction.
23 Ms. Mueller also has some impurities. In your opinion, you
24 said that was not a faithful reproduction. Somewhere in
25 between, you've drawn the line, some impurity level.

1 A. No, I said that hers was not a faithful reproduction
2 because of the mistakes she made in the synthesis. It
3 wasn't based on the impurity levels, although that was the
4 outcome.

5 Q. Yes. If you did know what the impurity or impurities
6 was, how much of it would you permit in the synthesis for it
7 to be a faithful reproduction?

8 A. I don't know. I'd have to assess that empirically
9 based on its effects on the transformation from Form B to
10 Form A.

11 Q. But you would set some requirements based on the
12 transformation of Form B to Form A?

13 A. Well, there must be a level of the particular
14 impurities or impurity that is inhibiting the transformation
15 on which it's effective.

16 Q. And above that level, it would not be a faithful
17 reproduction?

18 A. No, as I said, the faithfulness of the reproduction is
19 not based upon impurity level. It's based upon whether this
20 is carried out correctly and actually reproduces what the
21 patent teaches.

22 Q. Let's look at Example 25 again.

23 Example 25 doesn't set forth any requirement with
24 respect to impurity, right? Impurities?

25 A. It doesn't mention impurities in the example, no.

1 Q. So if the Court were to disagree with you that
2 Ms. Mueller did not faithfully reproduce Example 25, if the
3 Court were to disagree with your criticisms, and Ms. Mueller
4 reproduced Example 25 and got Form B, you would say that's a
5 faithful reproduction that produced Form B; right?

6 A. I don't think it is a faithful reproduction.
7 Obviously the Court will decide based on my evidence.

8 Q. Okay. But you wouldn't say it was not a faithful
9 reproduction based upon the fact that it contained
10 impurities.

11 A. It wasn't based on impurities that I said it wasn't a
12 faithful reproduction. It was based on mistakes.

13 Q. Dr. Steed, is it your opinion that it would be
14 impossible to faithfully reproduce Example 25 and not
15 generate enough impurities to get all Form B?

16 A. I'm sorry, would you repeat the question? Not
17 generate enough impurities? Sorry. Please repeat it.

18 Q. Sure. Let me rephrase it.

19 Isn't it possible that you could, notwithstanding
20 your opinion that Ms. Mueller did not faithfully reproduce
21 Example 25, isn't it possible that one could faithfully
22 reproduce Example 25 and get enough impurities to stabilize
23 Form B?

24 A. No.

25 Q. Why not? How do you know? Given that you don't know

1 the identity of the key impurity, how do you know that you
2 couldn't generate enough of it to stabilize Form B?

3 A. Because if you perform it as a chemist would, which is
4 to purify the material to the normal kinds of levels that
5 chemists do, if you're careful with your technique in the
6 way that I described and the way the Wisconsin scientists
7 were, then you would get a pure enough sample that Form B
8 wouldn't exist at room temperature.

9 Q. We looked at a document earlier, it was Plaintiff's
10 Exhibit 507, and we looked at the first sample of Form B,
11 and it had a relatively low level of impurities compared
12 with the other samples in that table; right?

13 A. It had a relatively low level of two particular
14 impurities.

15 Q. Two particular impurities.

16 Do you have any evidence to suggest that samples
17 with relatively low levels of impurities can't be Form B?

18 A. All the evidence seems to suggest that it's only
19 impure samples with relatively high levels of impurities
20 that are Form B. I don't think samples with low levels of
21 impurity can be Form B because they're transformed to A.

22 Q. We just talked about a sample of low levels of
23 impurities in Plaintiff's Exhibit 507.

24 MS. RANNEY: Maybe we can put it back up.

25 Q. Sample CEWS141/1; do you have any evidence that this

1 sample had high levels of other impurities?

2 A. These are levels of only two particular impurities,
3 one is actually the starting material, and we know that
4 isn't the one that stabilizes Form B, I don't think. So, we
5 don't know what the other levels of impurities are, but the
6 fact that it's Form B means there must be other impurities
7 stabilizing it.

8 Q. Do you have any empirical evidence that a sample with
9 low levels of impurities in general, not just these two, but
10 all, cannot be Form B?

11 A. A sample with low -- sorry. Please repeat the
12 question.

13 Q. Have you seen any empirical evidential that samples
14 with low levels of impurities in general can't be Form B?

15 A. Yes, I have. I refer back to the DSC x ray empirical
16 evidence that shows that samples with low levels of
17 impurities transform to Form A.

18 Q. Those were just DSCs for a few particular samples;
19 right?

20 A. They're samples with low levels of impurities because
21 they're transforming.

22 Q. Let's talk about the synthesis described in Example
23 25.

24 You might want to have the patent in front of you.
25 That's Defendants' Exhibit 752.

1 A. Okay. I still have it.

2 Q. All right. We discussed earlier that the goal of
3 Example 25 is to produce tapentadol hydrochloride, and
4 that's compound (-21); right?

5 A. Yes.

6 MS. RANNEY: Let's put up slide one of Plaintiff's
7 demonstrative.

8 Q. All right. There is compound (-21).

9 Now, in order to obtain this compound, Example 25
10 refers back to Example 24; right?

11 A. Yes.

12 Q. And it uses compounds minus one as a starting
13 material.

14 A. I believe so.

15 Q. If you look at Example 24, it starts with the compound
16 plus one; right?

17 A. That's right.

18 Q. So Example 25 refers back to Example 24, but it uses
19 the opposite enantiomer starting material.

20 A. Correct.

21 MS. RANNEY: Could you put up the three steps of
22 Example 24, please?

23 There it is, starting with step one.

24 Q. Now, going back to Example 25, you talked about the
25 starting material was minus one, and the example states that

1 that starting material was prepared according to Example 2;
2 correct?

3 A. Yes.

4 MS. RANNEY: Let's add that.

5 Q. Would you agree that this is the synthesis of Example
6 25 as stated in the '737 patent?

7 A. Yes, this is the synthetic method.

8 Q. Now, you've repeated an organic synthesis that someone
9 else has previously done; right, Doctor?

10 A. Yes.

11 Q. And you would agree that to faithfully reproduce such
12 a synthesis that someone else has done, you must follow
13 their procedures, even if you would normally do it a
14 different way; right?

15 A. If you're reproducing something then, you do it the
16 way -- the thing you're following.

17 Q. Okay. Now, you testified yesterday regarding work
18 performed in connection with this litigation at the
19 University of Wisconsin; right?

20 A. Yes.

21 Q. And you testified that the work resulted in a mixture
22 of Form A and Form B of tapentadol.

23 A. That's right.

24 Q. And do you recall that three percent of the starting
25 material remained in the product of the University of

1 Wisconsin's work?

2 A. Yes, that's right.

3 Q. You also testified yesterday that the University of
4 Wisconsin began its synthesis at step three of Example 24
5 with material purchased from a company called Norac.

6 A. Correct.

7 Q. Can we put that up on the screen?

8 Does that seem accurate to you, Professor?
9 University of Wisconsin began at step three with Example 24?

10 A. Yes.

11 Q. But Norac did not follow the steps disclosed in
12 Example 24 in order to make this starting material, did
13 they?

14 A. Their synthesis was the same is my understanding. So
15 I believe that they do the -- the (-22) intermediate I don't
16 think they isolate, but other than that, it's the same.

17 Q. The same.

18 A. That's my understanding, at least in terms of the
19 synthetic method.

20 Q. Okay. You told us something a little different at
21 your deposition.

22 There's going to be two pages. The first one is
23 237.

24 (A copy of the deposition was placed before the
25 witness.)

1 MR. FITZPATRICK: We have an additional copy, Your
2 Honor, if that would --

3 THE COURT: That would be great. Thanks.

4 MS. RANNEY: Oh. Sorry.

5 THE COURT: I just gave mine to the witness.

6 MS. RANNEY: Yes, thank you. I'm sorry about
7 that.

8 THE COURT: Thanks.

9 And by the way, with the dep transcript, any
10 issue? Any issue?

11 MR. HARP: No, Your Honor.

12 THE COURT: Thank you.

13 MS. RANNEY: We can go back a page, actually.

14 Q. And if you look at line 13, the question is: "And we
15 know that Norac did not follow the previous steps disclosed
16 in Example 24 beginning in -- on Column 18, nor did they
17 follow the making of the precursor, Example 2, beginning at
18 Column 7."

19 And you said: "I must admit, I don't know how
20 they -- how they got to their precursor 2. They may well
21 have followed Example 2, but I -- my understanding is their
22 synthesis was the same in concept, but with differences in
23 some nuances to get to this plus 23 compound, or minus 23 in
24 our case."

25 Did I read that correctly?

1 A. You did.

2 Q. Okay. And let's go to the next page. And you
3 understand we're talking about the same subject matter here,
4 whether Norac followed the steps of Example 24.

5 A. Indeed.

6 Q. And starting at line 13, there's a question:

7 "What I'm trying to do is, I'm just trying to be
8 very clear about what it is they did and what they didn't
9 do."

10 And your answer was:

11 "So my understanding is that the way in which they
12 made that minus 23 compound is the -- is a very similar
13 process to the earlier -- the earlier parts of Example 24,
14 but differs in some details."

15 A. Yes, that's right, that's what I was alluding to when
16 I said they didn't isolate the intermediate compound.

17 Q. But Norac did not follow the exact steps set forth in
18 Example 24; correct?

19 A. From my overview of the synthesis, it doesn't seem it
20 was exactly the same. Like I said, the same strategy, but
21 different in some nuances.

22 Q. Yes. You testified earlier that in order to
23 faithfully reproduce an organic synthesis that someone else
24 has done, one should follow the procedure that the other
25 person did; right?

1 A. Correct.

2 Q. And Norac did not follow that exact procedure.

3 A. Norac was attempting to reproduce Example 25. The
4 reproduction is step three that the University of Wisconsin
5 did. I think that's what we were talking about.

6 Q. The University of Wisconsin was attempting to
7 reproduce Example 25; right?

8 A. Step three of Example 25.

9 Q. Why was the University of Wisconsin only trying to
10 reproduce step three of Example 25 when the task was to
11 reproduce the entirety of Example 25?

12 A. No, the task was to identify what crystal form results
13 from the crystallization step at the end of Example 25, and
14 step three is the relevant step for that.

15 Q. Let me represent to you that the task was to
16 faithfully reproduce Example 25. Would you agree that means
17 to reproduce the entirety of Example 25?

18 A. Well, that wasn't the task. The task was to reproduce
19 step three of Example 25.

20 Q. Sorry, I am representing to you that the task was
21 actually to faithfully reproduce Example 25.

22 A. Okay. This is a hypothetical?

23 Q. Yes, it's a hypothetical.

24 A. Okay.

25 Q. And if that were the task, you would agree that the

1 University of Wisconsin should have gone back and done it
2 from the beginning; correct?

3 A. No, that would have been impossible because they
4 wouldn't have had any seed material to step one.

5 Q. There is synthesis in Example 2.

6 A. Correct.

7 Q. They could have gone back to that; right?

8 A. They could have, but in step one of Example 25, they
9 wouldn't have had any seed material, so it would have been
10 impossible for them to do.

11 Q. Couldn't the University of Wisconsin have gone back
12 further than they did?

13 A. They could have gone back, arbitrarily followed, they
14 would have had to purchase the seed material if they had
15 gone back to step one.

16 Q. Okay, but they could have started at Example 2; is
17 that right?

18 A. It depends on the object of the experiment. But you
19 can follow any published procedure. The published procedure
20 they were following was step three.

21 Q. Okay. But again, in my hypothetical, the goal is to
22 faithfully reproduce Example 25.

23 A. If you want to reproduce the whole of Example 25, then
24 you could in principle go and do that. You'd have to get
25 some seed material from somewhere.

1 Q. Okay.

2 We've spent a lot of time talking about impurities
3 and how they affect polymorphic form; right?

4 A. Yes.

5 Q. Now, given that the University of Wisconsin started
6 with step three of Example 24, isn't it possible that their
7 starting material could have had a different impurity
8 profile than if they had gone back and started at Example 2?

9 A. Well, we know exactly what the impurity profile of
10 their starting material was. It was pure material, and they
11 analyzed it.

12 Q. But it is possible that it could be different than
13 someone who had gone back and started from Example 2;
14 correct?

15 A. As Dr. Buschmann testified, one purifies these at each
16 step, so it should have been a pure material, and, indeed,
17 they proved that it was.

18 Q. But all samples have some impurities; right?

19 A. Yes.

20 Q. And isn't it possible that the key impurity that
21 stabilizes Form B could be introduced in the steps prior to
22 step three of Example 24?

23 A. I don't think so, no.

24 Q. You testified earlier that you don't know the identity
25 of this impurity or how much of it is required to stabilize

1 Form B; right?

2 A. Correct.

3 Q. Yet it's your testimony that it's impossible that this
4 impurity could be introduced prior to step three of Example
5 24?

6 A. It is my opinion that the impurity isn't introduced
7 there. After all, the University of Wisconsin also got some
8 Form B, so their step must have had some impurity introduced
9 to stabilize their Form B, too.

10 Q. They did get some Form B. Isn't it possible that more
11 of this impurity could have been introduced prior to Example
12 24 such that the University of Wisconsin would have gotten
13 all Form B?

14 A. I'm not sure I understand the question. Could you
15 repeat it, please?

16 Q. So the University of Wisconsin got some Form B in the
17 product of their Example 25?

18 A. Yes.

19 Q. So according to you, presumably, they had some of this
20 impurity.

21 A. Correct.

22 Q. Isn't it possible that had they gone back to Example 2
23 and started, there would have been more of this impurity
24 present?

25 A. So you're postulating that it would be the same

1 impurity introduced in at least two different places?

2 Q. Sure. We don't know what this impurity is. There
3 could be multiple impurities.

4 A. That doesn't make sense to me.

5 Q. All right. Let's move on to the reproductions of
6 Example 25 carried out by Ms. Marita Mueller.

7 MS. RANNEY: Can we put up slide nine of
8 Defendants' demonstrative?

9 Q. This is a slide you discussed yesterday in the context
10 of Ms. Mueller's reproductions of Example 25; right?

11 A. Yes.

12 Q. And on the left in blue is the column for Example 25,
13 and the steps one through five are listed.

14 A. Correct.

15 Q. And if we go on to slide 11, we have steps six through
16 10?

17 A. Correct.

18 Q. Dr. Steed, Example 2 is not on these slides; correct?

19 A. That's right.

20 Q. And neither are steps one or two of Example 24.

21 A. Correct.

22 Q. So this is just the third step of Example 25; correct?

23 A. That's right.

24 Q. And you've made 10 steps out of it.

25 A. I've broken down the recipe for step three into the 10

1 operations that are required, 10 operations, plus the
2 product.

3 Q. Okay. That's fine.

4 I just wanted to confirm one other thing. You
5 have a column for Grunenthal there with some X's in it.

6 A. Correct.

7 Q. Where you don't have an X, do you agree that
8 Ms. Mueller faithfully reproduced that step?

9 A. Yes, I do.

10 Q. Okay. Thank you.

11 All right. So looking at step one, you testified
12 yesterday that Ms. Mueller did not characterize the starting
13 material she used for step one; is that right?

14 A. I was going by what she herself said in her
15 deposition.

16 Q. Okay. And that was the primary basis for your opinion
17 that Ms. Mueller did not faithfully execute this step;
18 right?

19 A. She said in her deposition that she didn't analyze the
20 impurities in her starting material, and that she also
21 didn't use the same amount.

22 MS. RANNEY: Could we go to Defendants' Exhibit
23 1206 and page 110768?

24 Could you just highlight the title at the top
25 there?

1 Q. Doctor, this is the lab notebook page for
2 Ms. Mueller's first reproduction which resulted in
3 GB-Bu322-1-1.

4 THE COURT: I'm sorry, what's the exhibit number?

5 MS. RANNEY: Oh, I'm sorry. It's Defendants'
6 Exhibit 1206.

7 (G B-Bu322-had 1-1.

8 THE COURT: And the page on it?

9 MS. RANNEY: It's Bates 110768.

10 THE COURT: Oh, I see it. Okay. Thank you.

11 Q. So just to go back, this appears to be the lab
12 notebook page for Ms. Mueller's first reproduction, which
13 was titled GB-Bu-322-1-1; correct?

14 A. Correct.

15 Q. Okay. And if you look at where it says "Workup," I
16 believe -- I'm sorry, "Execution," and it says "mix Bu351
17 with HBR and stir for two hours while refluxing."

18 do you understand that Bu351 is the starting
19 material for this synthesis?

20 A. Yes.

21 Q. Okay.

22 MS. RANNEY: If you could just go to the previous
23 page, and highlight the title. I think it's the written
24 text there.

25 Q. So this is kind of hard to read, but it looks like it

1 says GB-Bu-351-1, and I'm going to represent that to you
2 that's what it says.

3 A. Yes, if you kind of catch it out of the corner of your
4 eye, it does.

5 (Laughter)

6 Q. All right. And if you go below there, it says "H-NMR"
7 down in the middle of the page?

8 A. Yes.

9 Q. This would indicate to you that Ms. Mueller
10 characterized her Bu351 starting material as proton NMR; is
11 that right?

12 A. Yes, that's right.

13 Q. And below that, if we can just go down a little more,
14 "Amount of Rotation," this would indicate that Ms. Mueller
15 characterized her starting material for optical rotation;
16 right?

17 A. Yes.

18 MS. RANNEY: Okay, and down a little more -- if we
19 can just highlight the second half of the page.

20 Q. And this looks like it was also characterized by
21 thin-layer chromatography; right?

22 A. Yes, that looks like a thin-layer chromatogram.

23 Q. I know it's hard to see.

24 A. I'm not sure what it's showing.

25 Q. Okay. But it was characterized by TLC, it looks like?

1 A. Looks like it.

2 Q. Okay. Do you still believe that Ms. Mueller did not
3 characterize her starting material?

4 A. She certainly characterized it in terms of being the
5 right molecule, and I think that's what she's implying by
6 the "OK" by H-NMR. She hasn't carried out an analysis of
7 its impurity profile, and I believe that's what she was
8 referring to, and what I was referring to.

9 Q. Okay. Does Example 25 instruct the reader to examine
10 the impurity profile of the Bu351 starting material?

11 A. No, it doesn't.

12 Q. Okay. And one last thing here. Would you read the
13 yield at the bottom of this page?

14 A. Yes.

15 Q. It's 4.545 grams, correct?

16 A. That's what it said -- oh, yes. I'm not quite sure
17 what the NE calls for, but that looks reasonable.

18 Q. Now, you also testified that Ms. Mueller used 4.55
19 grams of starting material for her Example 25 synthesis,
20 whereas the patent specifies 4.3 grams; right?

21 A. Correct.

22 Q. And presumably, the reason Ms. Mueller used 4.55 grams
23 was that that was the yield from the previous step?

24 A. Well, without being able to be in her head, I don't
25 know, but that seems reasonable.

1 Q. And Ms. Mueller performed this step; right?

2 A. Performed which step?

3 Q. Performed this step creating the starting material,
4 the (-23) compound, which was Bu351.

5 A. Yes, she had the starting material.

6 Q. And this was a step that the University of Wisconsin
7 didn't perform; right?

8 A. They personally didn't make it. I mean, it was made
9 by another chemist by a similar procedure, and then they
10 started from there with their reproduction, step three.

11 Q. Okay.

12 MS. RANNEY: Could we go back to the table sort of
13 near the top of this document?

14 Actually, let's go to the next page.

15 Q. Okay. Again, this is the page for the actual
16 synthesis of Bu-322-1-1.

17 MS. RANNEY: If you could highlight that table.

18 Q. And you see there where it says batch size of
19 Bu-351-1-1, and the mass in grams is 4.55.

20 A. Right.

21 Q. And you see the volume of aqueous HBR, hydrobromic
22 acid, is 111.47?

23 A. Yes.

24 Q. And I believe the value in the patent for hydrobromic
25 acid was a hundred milliliters; correct?

1 A. Yes.

2 Q. So Ms. Mueller appears to have scaled up her
3 experiment to account for the larger mass of starting
4 material; is that right?

5 A. Yes, she does.

6 Q. Do you have any reason to believe that Ms. Mueller did
7 not scale up the rest of her experiment to account for this
8 larger value of starting material?

9 A. I must say I haven't checked through to see whether
10 the other numbers are scaled up, but that would seem
11 reasonable.

12 Q. Let's go back to the Defendants' demonstratives, slide
13 nine.

14 Okay. You also have a red X next to step four,
15 which is, the "The residue was treated with concentrated
16 sodium hydrogen carbonate solution until an alkaline
17 reaction was obtained."

18 Is that right? Did I read that correctly?

19 A. Yes.

20 MS. RANNEY: Okay. Could we go back to
21 Defendants' Exhibit 1206, please, and highlight the "Workup"
22 section?

23 Q. And here it says, "render the residue alkaline with
24 concentrated sodium hydrocarbonate solution." Is that
25 right?

1 A. Yes.

2 Q. You testified yesterday that Ms. Mueller did not
3 measure that, record a pH here.

4 A. That's correct.

5 Q. And for that reason, you don't believe that she
6 actually did render the residue alkaline?

7 A. I pointed out that it was a potential problem. If it
8 was only just alkaline, it may not be enough to properly
9 kill off the hydrobromic acid, so it was a question mark.

10 Q. Just a question mark.

11 MS. RANNEY: Could we go back to Defendants'
12 demonstratives?

13 Let's go actually onto slide 10.

14 Q. You used this slide to demonstrate how an extraction
15 process works; right?

16 A. Correct.

17 Q. This was a dichloromethanic extraction?

18 A. Correct.

19 Q. Could you just explain briefly again how that works?

20 A. Sure.

21 So the mixture of the water solution which
22 contains the product and the neutralized hydrobromic acid
23 and all the impurities and everything is placed into the
24 separating funnel along with the 50 milliliters of
25 dichloromethane, and the two are mixed together. They form

1 two layers, as it shows in the diagram here. And in this
2 particular case, because we have -- because the water
3 solution is saturated with a salt, sodium bromide in this
4 case, it will actually be the more dense layers that will be
5 on the bottom. Normally we chemists would realize
6 dichloromethane is more dense, so usually that will be on
7 the bottom, but in this particular case, we have so much
8 salt, it inverts the density order. So the aqueous layer is
9 on the bottom. The chemist opens the tap and drains off the
10 aqueous layer into the receiving flask, makes a decision as
11 to when the layer boundary is passing through the tap, turns
12 the tap off, stops the flow, changes the receiving flask,
13 and then puts the dichloromethane layer into another
14 receiving flask, and then because we're extracting twice
15 into two lots of 50 milliliters of dichloromethane, then the
16 aqueous layer has to go back into the separating funnel, add
17 more dichloromethane mix, repeat the separation, combine the
18 two organic layers.

19 Q. Okay. One last question on Ms. Mueller's experiment.

20 You don't dispute that Ms. Mueller obtained
21 tapentadol hydrochloride?

22 A. She certainly got some.

23 Q. Let's move on to your obviousness opinions.

24 MS. RANNEY: Could we put up Defendants' Exhibit
25 755?

1 All right. If you would just highlight the title
2 and authors.

3 Q. This is one of the documents you have testified about
4 in rendering your opinion that the '364 patent is obvious;
5 right, Doctor?

6 A. Correct.

7 Q. And at the bottom of the first column of page 945,
8 could you read the sentence beginning "Solid drug
9 substances"?

10 A. Sure. "Solid drug substances display a wide and
11 largely unpredictable variety of solid state properties.
12 Nevertheless, application of basic physicochemical
13 principles combined with appropriate analytical methodology
14 can provide a strategy for scientific and regulatory
15 decisions related to solid state behavior in the majority of
16 cases."

17 Q. Do you disagree with the statement that solid drug
18 substances display a wide and largely unpredictable variety
19 of solid state properties?

20 A. No, I don't disagree with it.

21 Q. Can we go to Defendants' Exhibit 930? Just highlight
22 the title and authors.

23 Q. You also testified about this paper yesterday, Doctor.

24 A. Correct.

25 MS. RANNEY: All right. Can we put up page 276 on

1 the left and 277 on the right?

2 Highlight the last paragraph in column -- on page
3 276, and then continuing onto the end of the paragraph
4 there.

5 Q. Sorry, I know this is kind of long, but could you just
6 read this into the record.

7 A. Not a problem.

8 "Despite more than a century of research, the
9 fundamental mechanisms and molecular properties that drive
10 crystal form diversity, specifically the nucleation of
11 polymorphic forms, are not well understood. As a result,
12 predictive methods of assessing polymorphic behavior of
13 pharmaceutical compounds by ab initio calculations remain a
14 formidable challenge. Even in cases where the existence of
15 a crystalline form is predicted, the stability relative to
16 other crystalline packing arrangements has been difficult to
17 estimate with accuracy. Moreover, the prediction of packing
18 structures for multicomponent, e.g., solvates, hydrates,
19 co-crystals, or ionic systems is not yet possible."

20 Do you want me to stop there?

21 Q. Could you just read the last sentence?

22 Sorry.

23 MS. RANNEY: Pull it up.

24 A. Sure.

25 "Due to these limitations solid form discovery

1 maintains remains an experimental exercise, where manual
2 screening methods are employed to explore form diversity of
3 a compound."

4 Q. Do you agree with the statements in this paragraph,
5 Doctor?

6 A. Yes.

7 Q. Okay.

8 MS. RANNEY: And can we go to page 296?

9 Q. In the first full paragraph on the second column,
10 could you read the sentence beginning, "Unlike salts?" It's
11 kind of in the middle of the paragraph.

12 A. Okay.

13 "Unlike salts, which for the most part can be
14 prophetically claimed based on an understanding of the
15 chemical structure of the compound and its ionization
16 constants, the existence and identity of hydrates, solvates,
17 co-crystals and polymorphs have defied prediction.

18 Therefore, in order to obtain patent protection on these
19 forms, some of which may have significantly different
20 properties and relevance as development candidates, it is
21 essential to prepare them, identify conditions for making
22 them and evaluate their properties as valuable new
23 pharmaceutical materials."

24 Q. Do you agree that hydrates, solvates, co-crystals and
25 polymorphs have defied prediction at the time of this

1 article?

2 A. Yes, there's a difference here between calculation and
3 computational prediction in advance based on the chemical
4 structure and actually simply carrying out the experiment
5 and isolating the crystals. So this is very much an
6 empirical science, although there have been some very nice
7 recent advances in computation prediction.

8 Q. This is as of 2004, though; right?

9 A. Yes.

10 Q. Okay. Thank you.

11 MS. RANNEY: Let's put the '737 patent back up,
12 Defendants' Exhibit 752.

13 Q. At the top right, you see that it says "Date of
14 Patent, June 19th, 2001"?

15 A. Yes.

16 Q. And you understand this to be the issue date of the
17 '737 patent?

18 A. Yes.

19 Q. Prior to June of 2001, there weren't any patents or
20 publications described in the polymorphic forms of
21 tapentadol hydrochloride, were there?

22 A. Not that I'm aware of.

23 Q. You've reviewed the '737 patent; right?

24 A. Yes.

25 Q. Do you have any sense of how many compounds this

1 patent covers? Order of magnitude?

2 A. There were 28 examples, and then there's a Markush
3 structure.

4 Q. Okay. And there's no disclosure in the '737 patent
5 that any of these claimed compounds exist in more than one
6 crystal form, is there?

7 A. No, the '737 is not directed to crystal forms.

8 Q. Right. In fact, there's no discussion of polymorphism
9 at all in the '737 patent.

10 A. Not that I'm aware of.

11 Q. Now, there's no reason to believe that all the
12 compounds in the '737 patent will be polymorphic; right?

13 A. The chances will be about 50 percent.

14 Q. That all of them would be polymorphic? There could be
15 millions of compounds in this patent.

16 A. When polymorphs have been studied, about 50 percent of
17 them turn out to have more than one form. On average.

18 Q. That's for each individual polymorph.

19 A. If you take any particular given compound, there's
20 about a 50 percent chance it will be polymorphic or have
21 some kind of other crystal form.

22 Q. Okay. For the compounds in this patent that do have
23 polymorphs, will each of them have the same number of
24 polymorphs?

25 A. No.

1 Q. Will they all have the same types of crystal form?

2 A. Without empirically screening, we don't know.

3 Q. You have to empirically screen to find out.

4 A. Yes.

5 Q. Okay. Looking at the '737 patent, there's nothing in
6 particular that would motivate a person of ordinary skill in
7 2004 to select tapentadol hydrochloride as a compound for
8 further study; correct?

9 A. Tapentadol hydrochloride is not singled out amongst
10 the examples.

11 Q. Let's look at Example 25 in Column 20.

12 And you recognize this structure to be tapentadol
13 hydrochloride, of course.

14 A. Yes.

15 Q. Now, it wouldn't be possible for a person of ordinary
16 skill in 2004 to look at this structure and definitively say
17 that tapentadol hydrochloride is polymorphic, would it?

18 A. Certainly not definitively. You could -- you could
19 make some educated guesses based on the fact that it's got
20 some hydrogen bonding propensity.

21 Q. If you could somehow predict that tapentadol
22 hydrochloride was polymorphic, there's no way to predict
23 that one of its forms would be monoclinic, is there?

24 A. No, you wouldn't predict the particular crystal
25 structures. As I said, you would simply empirically screen

1 for them and then find out from the crystals.

2 Q. And there's no way to predict how many forms
3 tapentadol hydrochloride might have, is there?

4 A. No, as I said, crystal structure prediction using a
5 computer by calculation is still in its infancy.

6 Q. Is there any way in 2004 to predict what the most
7 stable form would be?

8 A. Without actually doing the empirical screening, no.
9 This is the way we -- crystallographers proceed is by
10 empirical testing.

11 Q. You can never know for certain that you have obtained
12 the most stable polymorphic form of a given compound, can
13 you?

14 A. No, you can never be absolutely certain, that's right.

15 Q. And you can never know for certain whether you have
16 discovered all the polymorphic forms of a given compound,
17 can you?

18 A. That's right. There's always the faint chance that
19 there's some other polymorphic form that has not yet been
20 discovered. Obviously as a compound is studied more and
21 more, that becomes vanishingly small as a possibility.

22 Q. So there could be other forms of tapentadol
23 hydrochloride out there?

24 A. There could be. That would be interesting.

25 Q. Let's go to Defendants' Exhibit 304.

1 This is the '364 patent; right?

2 A. Yes.

3 Q. Do you see in the first column where it says "Foreign
4 Application Priority Data"?

5 A. Yes.

6 Q. And next to EP 0401 5091, it says June 28, 2004.

7 A. Yes.

8 Q. You understand that's the priority date of the '364
9 patent.

10 A. Yes.

11 Q. And between June 2001, when the '737 patent issued,
12 and June 2004, there weren't any patents or publications
13 describing the polymorphic forms of tapentadol, were there?

14 A. Not that I'm aware.

15 Q. Would you agree that the first time polymorphic was
16 mentioned in relation to tapentadol hydrochloride was when
17 the '364 patent was published?

18 A. I believe so, yes.

19 Q. Let's go to Defendants' Exhibit 974.

20 Do you recall testifying about this document
21 yesterday, Dr. Steed?

22 A. Yes.

23 Q. And do you recall this is Dr. Buschmann's lab notebook
24 entry for batch zero?

25 A. Yes.

1 MS. RANNEY: Could we go to the last page of the
2 document? It's Bates 18951.

3 Q. Do you see the structure at the top left there?

4 A. Yes.

5 Q. Can you just confirm for me that that structure is
6 tapentadol hydrochloride?

7 A. Yes, I believe it is.

8 MS. RANNEY: Let's go to Plaintiff's Demonstrative
9 slide 2.

10 Q. And you might want to have the '737 right in your
11 binder. If we need to put it up on the screen, we will.

12 So I've put up a copy of slide 4 of your
13 demonstratives on the screen. Do you recognize this?

14 A. Yes.

15 Q. And these are the same steps depicted in your expert
16 report; right?

17 A. I'd have to refresh my memory, but I believe so.

18 Q. The product of Example 25, of course, and the product
19 of step three of your diagram is tapentadol hydrochloride;
20 is that right?

21 A. Right.

22 Q. And this is compound (-21) in the '737 patent.

23 A. Right.

24 MS. RANNEY: Can we go to the next slide? I've
25 just rearranged your steps to make a little more room.

1 These are the same steps. It's from the previous slide.

2 And can we go ahead and put up compound (-21)?

3 Q. This compound is tapentadol hydrochloride. It's the
4 same compound that is the product of your step three; is
5 that right?

6 A. Yes.

7 Q. Let's see how we get there.

8 We talked earlier about how the starting material
9 for Example 25 is (-1) or at least the starting materials
10 for step one of Example 24.

11 A. Okay.

12 MS. RANNEY: So let's put that up.

13 Q. Now, you see this is compound (-1).

14 A. Okay.

15 Q. Now, this is not the same compound as starting
16 material for your step one, is it?

17 A. I'd have to go check. Are you suggesting the
18 stereochemistry is different?

19 Q. Yes, if you wouldn't mind just checking right now.

20 A. Yes, it's a little bit difficult to do in the head on
21 a witness stand. They're complicated, three-dimensional
22 manipulations. I can't remember. When I drew the synthesis
23 out, I drew it out just based on the diagrams, for example,
24 24 or 25. So maybe my diagram refers to Example 24 because
25 that's got all three pictures in it. So if it's the other

1 way around, that will be why.

2 Q. Well, steps one, two, and three these are steps one,
3 two, and three of Example 24; right?

4 A. Well, these are the three synthetic steps of both
5 Example 24 and 25. I can't remember if I drew the diagrams
6 based on 24 or 25, and I must admit on the witness stand I'm
7 not -- not able to do the 3D in my head.

8 Q. Absolutely.

9 You have the product of Example 25 here, not
10 Example 24.

11 A. Okay.

12 Q. You have tapentadol hydrochloride, which is (-21).

13 A. Okay.

14 Q. And this should have started with (-1). But let's go
15 ahead and do it now.

16 If you look at the ether chain on your starting
17 material and compound (-1), it's in the plane of the screen;
18 right?

19 A. The ether chain? What's the ether chain?

20 Q. It's the short chain -- see where the OH strip is?
21 It's across from that.

22 A. Are you able to point?

23 Q. Oh, yes. Sorry.

24 This guy here.

25 A. Okay.

1 Q. It's in the plane of the screen, right, and it's in
2 the plane of the screen in compound (-1). Right? Not going
3 out or into the screen.

4 A. Sorry. Repeat the question, please.

5 Q. This chain here is in the plane of the screen in this
6 diagram; right?

7 A. Are you referring to the ethyl group?

8 Q. Yes.

9 A. Okay.

10 Q. And it's in the plane of the screen in compound (-1);
11 right?

12 A. I guess so, yes.

13 Q. Okay. And the longer chain with the dimethylamino
14 group, it's also in the plane of screen; right?

15 A. Okay.

16 Q. And it's also in the plane of screen here in compound
17 (-1).

18 A. Okay.

19 Q. But here, in your compound, you have the aromatic ring
20 coming out of the screen; right? Or, sorry, going into the
21 screen.

22 A. Going backwards, right.

23 Q. Sorry. And over here, it's coming out.

24 A. Okay.

25 Q. So the stereochemistry in these two compounds is

1 different; correct?

2 A. I must admit here on the witness stand I can't do it.
3 I usually use a model. If I made an error in the
4 stereochemistry, I'm happy to put my hands up.

5 Q. You reviewed these slides before you brought them to
6 the courtroom with you; right?

7 A. I did. Really, the point of this was to look at the
8 actual chemistry that's going on. I must admit I didn't sit
9 down with my models and do the RS assignments when I checked
10 them through.

11 Q. Okay. But you've testified about this slide in quite
12 a bit of detail yesterday, right?

13 A. The point was that I testified, actually not in a
14 great deal of detail, from the point of view of the chemical
15 transformations going on. Like if the stereochemistry is
16 wrong and I can't see where it is, I hold my hands up.

17 Q. Okay. You also testified about step two; right?

18 A. Correct.

19 Q. And I believe the Judge asked a question about the
20 stereochemistry at that point.

21 A. That's right.

22 Q. And you said that there was some sort of inversion of
23 the stereochemistry in the step.

24 A. Yes, in terms of the Cahn Ingold prelog rules, they're
25 based on the atomic weight, and so the chlorine takes

1 priority one in the compound on the left, whereas the
2 hydrogen that replaces it would take priority four in the
3 compound on the right.

4 Q. You were here for Dr. Buschmann's testimony; right?

5 A. Correct.

6 Q. Did you hear Dr. Buschmann testify that there is no
7 inversion of stereochemistry in this step?

8 A. I think what he was implying was that the chlorine and
9 the hydrogen go into the same place without the carbon
10 inverting.

11 Q. You've drawn an inversion here. Here, the aromatic
12 ring is going into the screen, and here, it's coming out;
13 right?

14 A. It may be. If I've made a mistake, I hold my hands
15 up. I must admit I didn't check the stereochemistry in
16 detail before I put the slides up. The purpose wasn't to
17 show stereochemistry at all.

18 Q. Okay. But you didn't correct this mistake, of course,
19 when we were talking about it yesterday.

20 A. Well, I didn't do the stereochemistry in my head.
21 It's quite complicated.

22 MS. RANNEY: Okay. Thank you, Dr. Steed. I have
23 no further questions.

24 THE WITNESS: Thank you.

25 THE COURT: Thank you very much.

1 Counsel, anything further?

2 MR. HARP: Just a few questions, Your Honor.

3 THE COURT: Yes. Go right ahead.

4 REDIRECT EXAMINATION

5 BY MR. HARP:

6 Q. Good morning, Professor Steed.

7 A. Good morning.

8 Q. You were asked a number of questions about the
9 impurity levels of samples of tapentadol. Do you recall
10 that this morning?

11 A. Yes.

12 Q. Do we have the benefit of testing Dr. Buschmann's or
13 Ms. Mueller's samples anymore?

14 A. No, we don't. The samples don't exist is my
15 understanding.

16 Q. And are you aware of any Form B samples -- for any
17 Form B sample that does not have impurities?

18 A. No, I'm not.

19 Q. If you could turn to Defendants' Exhibit 995, please,
20 page 10 of that exhibit.

21 MR. HARP: If we go actually down to the next
22 paragraph. Blow up the table as well, please.

23 Q. You were asked some questions this morning about the
24 table at the bottom of the page there.

25 A. Yes.

1 Q. What does the text of the document say about the
2 effect of an impurity on Form B?

3 A. Reading from this?

4 Q. Yes.

5 A. "All experiments gave CG5503 solid material in greater
6 than 84 percent yield. In the experiments in which no seeds
7 were used a mixture of Form A and B were obtained. Higher
8 amounts of GRT0912Y were observed to have a larger influence
9 on the formation of polymorph B than GRT4045Y."

10 Q. And what do you conclude from that statement about the
11 fact of the impurity on the formation of Form B?

12 A. So in these particular experiments, Crystallics are
13 concluding that this particular impurity GR0912Y had more of
14 an influence on the formation of Form B than the other
15 impurity they looked at.

16 Q. You were also asked this morning a number of questions
17 about the three steps that are laid out in Example 25;
18 correct?

19 A. Correct.

20 Q. Of those steps in Example 25, which one is important
21 to determine how the polymorphs are made?

22 A. It's not made until the very end of step three, so
23 it's only step three that's of relevance to the polymorphic
24 form.

25 Q. And why is that?

1 A. Well, because up until that point, there isn't even
2 any tapentadol present, and the tapentadol is not present in
3 solid form and hence crystalline form until the very end of
4 that step.

5 Q. How difficult is it in your field to do a polymorph
6 screen?

7 A. Really quite straightforward. I mean, in principle,
8 one experiment is the beginning of a polymorph screen:
9 Dissolve compound, evaporate solvent, analyze crystals that
10 result. Of course, that will be a very limited screen, and
11 typically, you would want to use perhaps a hundred different
12 crystallizations or even more.

13 Q. You've seen a number of crystallizations that have
14 been performed by Grunenthal and Crystallics or SSCI
15 regarding tapentadol.

16 A. Correct.

17 Q. And after all the work that has been done by
18 Grunenthal, Crystallics, and SSCI, how many forms of
19 tapentadol have been identified?

20 A. Two.

21 MR. HARP: Nothing further, Your Honor.

22 THE COURT: Thank you very much.

23 Anything further?

24 MS. RANNEY: Sorry. Just real quickly.

25 THE COURT: Yes. Go ahead.

1 RECCROSS EXAMINATION

2 BY MS. RANNEY:

3 Q. Dr. Steed, your counsel asked you if you were aware of
4 any samples of Form B with no impurities; is that right?

5 A. I've already forgotten the question.

6 Q. Sorry. He just asked you if you were aware of any
7 samples of Form B without impurities.

8 **A. Okay.**

9 Q. And you said that you were not.

10 A. That's right.

11 Q. Are you aware of any samples of Form A without any
12 impurities?

13 A. Well, as I testified before, all chemical substances
14 have small amounts of impurities.

15 MS. RANNEY: Thank you.

16 Nothing further.

17 THE COURT: Thank you.

18 Anything else?

19 MR. HARP: No, Your Honor. Thank you.

20 THE COURT: No? All right.

21 Dr. Steed, your testimony is complete here. Thank
22 you very much.

23 THE WITNESS: Thank you, Your Honor.

24 THE COURT: We do appreciate your time here with
25 us.

1 (Witness excused)

2 THE COURT: All right. I think at this point,
3 it's a good time for a five-minute break before we start
4 with the next witness. All right? So five minutes.

5 Thank you.

6 THE COURT CLERK: All rise.

7 (Recess taken)

8 THE COURT CLERK: All rise.

9 THE COURT: Have a seat, everyone.

10 Are we ready to move on with the next witness?

11 MS. SHARKEY: Yes, Your Honor.

12 I'm Lauren Sharkey, again, Your Honor.

13 And the Defendants would now like to call Dr. Adam
14 Matzger.

15 THE COURT: Thank you. And, I'm sorry, you're
16 representing?

17 MS. SHARKEY: All Defendants are calling Adam
18 Matzger, but I'm for Roxane Labs.

19 THE COURT: Thank you.

20 MS. SHARKEY: May we approach?

21 THE COURT: Yes, of course. We'll have the
22 witness sworn in.

23 THE COURT CLERK: Raise your right hand, place
24 your left hand on the bible.

25

1 A D A M M A T Z G E R, called as a witness on behalf of
2 the Defendants, and having been duly sworn, testified as
3 follows:

4 THE COURT CLERK: If you can step up and state
5 your name for the record.

6 THE WITNESS: Adam Matzger, M-a-t-z-g-e-r.

7 THE COURT: Counsel, taking a look at the exhibits
8 and the demonstratives, are there any issues?

9 MR. GLANDORF: There's an exhibit in here, 1097,
10 that we objected to on foundational grounds several times
11 now and it still has never been used, so I think we'll
12 maintain that same objection until we see it used.

13 THE COURT: And then we'll discuss it. All right.
14 Sound good.

15 MS. SHARKEY: I'll say initially, Your Honor, it's
16 a Grunenthal document, the bottom of it has the folder
17 location of where it was filed at Grunenthal so I'm not
18 really sure what they're disputing.

19 In any event, though, I have another document that
20 corroborates the information from -- authored by an inventor
21 on the patent, so I'm willing to give that out, but it was
22 the German original, and I'm trying to avoid putting
23 translations and German originals into the record here.

24 THE COURT: All right. Do you have copies for
25 everyone?

1 MS. SHARKEY: I have copies for everyone. I can
2 give that to them if that assuages their issue.

3 THE COURT: Why don't we do that so they have a
4 chance to take a look at it?

5 So you think you're going to be using the
6 document, then?

7 MS. SHARKEY: I am, and it's just a section of the
8 document, which the information is also in this document as
9 well, so...

10 These are marked DTX 1164 and DTX 1163.

11 And if it's all right, I can approach, Your Honor.

12 THE COURT: Yes, please do.

13 MS. SHARKEY: So, is it fine to proceed?

14 THE COURT: Let me hear. Any response?

15 MR. GLANDORF: We still have the same objection.

16 He's not a fact witness. We'd like to be able to lay a
17 foundation for it directly. If he had relied on this
18 document or either of these documents in his expert report,
19 we understand as an expert he can do that, but I don't
20 believe he did. So we would maintain our objection.

21 THE COURT: All right. So be prepared for a
22 foundation discussion and argument here.

23 MS. SHARKEY: Okay.

24 THE COURT: All right. Let's start.

25

1 DIRECT EXAMINATION

2 BY MS. SHARKEY:

3 Q. Okay. Can you please state your name for the record?

4 A. Adam Matzger.

5 Q. Good morning, Dr. Matzger. Did you prepare some
6 slides today to aid in your testimony?

7 A. Yes, I did.

8 Q. And are these them right here?

9 A. Yes, these are the documents.

10 Q. Okay. Now, in your binder -- you should have a binder
11 in front of you. Can you turn to DTX 135?

12 A. Okay. I'm there.

13 Q. And what is this document, Dr. Matzger?

14 A. So this is my curriculum vitae.

15 Q. And does this CV accurately reflect your background
16 and academic experience?

17 A. Yes, it does.

18 Q. And have you prepared a few slides for us today
19 summarizing this information?

20 A. Yes, I have.

21 Q. All right. Dr. Matzger, can you summarize your
22 educational background?

23 A. So after my undergraduate work at Oberlin College, I
24 went to the University of California at Berkeley, where I
25 obtained my Ph.D. in chemistry. After that, I went home to

1 Cal Tech, where I conducted postdoctoral studies, and then I
2 began my independent career in 2000 at the University of
3 Michigan in Ann Arbor, where I'm currently the Charles G.
4 Overberger Collegiate Professor of Chemistry in the College
5 of Literature, Sciences and the Arts, and I also hold an
6 appointment in the College of Engineering in macromolecular
7 science and engineering.

8 Q. And what courses do you teach at the school?

9 A. So I teach courses at the undergraduate and at the
10 graduate level. The undergraduate level, I mainly teach
11 courses about organic chemistry. At the graduate level,
12 I've taught a number of courses on the characterization of
13 materials, solid state chemistry, spectroscopic courses, as
14 well as some courses about polymer chemistry and other
15 topics.

16 Q. Moving on to slide five, do you publish any papers in
17 this field?

18 A. So my publications so far are over 150 in
19 peer-reviewed journals. These papers have collectively
20 garnered over 10,000 citations, and I have past experience
21 as a member of the editorial advisory board of the Journal
22 of Pharmaceutical Sciences, and I am currently an associate
23 editor for the American Chemical Society journal, Crystal
24 Growth & Design.

25 Q. And have you received any awards for your work or

1 research?

2 A. So I have. Most recently, I received the American
3 Chemical Society Akron Prize. I've also received the Alfred
4 P. Sloan Foundation Fellowship, an AAAS Fellowship, and then
5 earlier in my career, I have the 3M Untenured Faculty Award,
6 Beckman Award, and Ralph E. Pound, Jr. Faculty Award.

7 MS. SHARKEY: Your Honor, Roxane and other
8 Defendants offer Dr. Adam Matzger as an expert in organic
9 materials in solid state and managed and prepared materials.

10 THE COURT: Thank you.

11 Any objection?

12 MR. GLANDORF: No objection.

13 THE COURT: All right. He is so admitted as an
14 expert in those fields.

15 Thank you.

16 BY MS. SHARKEY:

17 Q. Can you please turn now to DTX 304 in your binder?

18 A. Okay.

19 Q. And what is this document?

20 A. So this is the '364 patent which I have considered,
21 especially in formulating my opinions about utility, but
22 also other aspects here.

23 Q. And have you prepared a slide today to summarize what
24 you believe the '364 patent relates to?

25 A. Yes, I have.

1 So the '364 patent relates to Form A of tapentadol
2 hydrochloride, and it's claimed that this is different from
3 Form B, which is purported to be obtained by the procedure
4 Example 25 of what we'll call the '737 patent.

5 Q. And looking back at the face of the patent, what are
6 the pertinent dates you'd like to point out to us?

7 A. So the first is the priority date, which is June 2004,
8 and then the issue date, which is August 2011.

9 Q. Are you aware of the claims of the '364 that are
10 asserted in this case?

11 A. There are four claims that are asserted, but let me
12 actually first give a timeline for where the '364 patent and
13 '737 patent, how these relate.

14 So the '737 patent, which is the one that
15 describes Example 25 that is stated to produce Form B, so
16 that date is 1994, and then Form A, the present patent that
17 we're talking about, the '364, that's the one that was filed
18 in 2004.

19 So with regard to the claims, there are four
20 claims that are in question here. The claims all relate to
21 crystalline Form A of tapentadol hydrochloride, and each of
22 the claims also refers to powder x ray diffraction data as
23 evidence of the identity of that Form A.

24 Q. Now, in coming to your opinions today, did you
25 consider the definition of a person ordinarily skilled in

1 the art?

2 A. Yes, I did. So my definition is somebody that would
3 have -- probably this would be a chemist or a chemical
4 engineer, somebody in a similar field who has experience in
5 development, preparation, characterization of polymorphic
6 forms of compounds. Such a person might well have a Ph.D.
7 or a Master's degree. If they had a Bachelor's, I would
8 expect that they would have a correspondingly longer
9 experience, maybe five to 10 years of relevant work
10 experience to be considered of ordinary skill in the art.
11 And, of course, the person would have knowledge of the
12 literature as of June 2004, the relevant date.

13 This is also -- I should point out the definition
14 that's offered by Professor Bernstein is substantially
15 similar to this, and my analysis doesn't hinge on which
16 definition is adopted.

17 Q. Thank you.

18 Now, let's get into some of the opinions that
19 you'll be offering today. Did you prepare a slide to
20 summarize these opinions?

21 A. I did. And so initially, I'll be discussing the issue
22 of utility, and the fact that the '364 patent specification
23 does not support the asserted utility. I'll then discuss
24 the issue of misleading statements that were made to the
25 USPTO under the general heading of unclean hands, and then I

1 will finish with a discussion of Marita Mueller's attempts
2 to recreate Example 25 of the '737 patent and how this
3 cannot be used as a basis to say that Form B alone is
4 produced.

5 Q. Thank you.

6 Let's start with that first one.

7 Have you created a slide today to show your
8 understanding of the legal standard for -- of your
9 understanding of the legal standard in this realm?

10 A. Yes, and I'm certainly not a lawyer, so I've -- I've
11 relied on these definitions.

12 My understanding of utility was pretty much
13 limited to, a patent needs to be useful, the subject matter
14 needs to be useful for patenting, but there are some other
15 subtleties which are here. So that utility is determined as
16 of the effective filing date is an important issue, and that
17 if one of skill in the art would not accept without question
18 the statements, there really should -- there's an
19 expectation of evidence to support the statements.
20 Conclusory statements are not sufficient.

21 Q. Thank you.

22 So let's look back now at DTX 304. That's the
23 '364 patent. You have that in front of you?

24 A. Yes.

25 Q. So what do you understand are the alleged disclosure

1 of utility in the '364 patent?

2 A. Okay. So there's a slide that shows the statement of
3 utility. So the statement of utility is: "Crystalline Form
4 A according to the invention has the same pharmacological
5 activity as Form B but is more stable under ambient
6 conditions. It can be advantageously used as active
7 ingredient in pharmaceutical compositions."

8 And as support that this is the utility claimed
9 for the patent, I've also shown here the pretrial brief, the
10 Plaintiffs' pretrial brief where they essentially say the
11 same thing, they say this is the utility of the patent.

12 Q. And, Dr. Matzger, did you reach any conclusions about
13 whether a person of ordinary skill in the art would have
14 questioned this statement of utility?

15 A. Yes, I think there are a number of questions around
16 the utility of this patent. This statement does not support
17 utility of the patent.

18 Q. And before we get into that, what analysis did you
19 undertake today and before today to arrive at these
20 conclusions?

21 A. So for utility, I just looked at the '364 patent
22 itself. So I confined my analysis to what was in the '364
23 patent, so that's what I'll be focusing on there, and then
24 we'll introduce other documents as we move on to the other
25 sections of my testimony.

1 Q. And so did you prepare a slide today to address your
2 concerns with this statement?

3 A. Yes, and that's the next slide.

4 Q. We have that. Slide 20.

5 A. So really, the statement is not something that would
6 be accepted without question. The issue is, there's no data
7 that supports the alleged utility, and so this leads me to
8 conclude that the '364 patent fails to demonstrate
9 sufficient utility.

10 Q. Okay. On that first point, let's look at slide 22.

11 How do you interpret this statement here?

12 A. Okay. So this is sort of the crux of the issue how to
13 interpret the utility here. So it says that "Crystalline
14 Form A according to the invention has the same
15 pharmacological activity as Form B but is more stable under
16 ambient conditions."

17 So we need to talk a little bit about what ambient
18 conditions means.

19 Itself, ambient conditions describes temperature,
20 pressure, and humidity, so it's a suite of conditions, it's
21 not just temperature and it's not just humidity. And so
22 that term, ambient conditions, is reasonably well defined,
23 but it's not defined what aspect of the ambient conditions
24 this is allegedly more stable under.

25 Stable is not very well defined, so there are many

1 different types of stability, and I have some slides to
2 discuss those. In reading the statement, one can't know
3 what type of stability is being referred to here.

4 Q. And here on slide 23, what is this type of stability?

5 A. So this stability is stability towards hydration, so
6 this is actually a pretty big issue in pharmaceutical
7 manufacture. Different polymorphs, different solid forms
8 can have different propensities to take up water. And so
9 here is a crystalline form just where the molecules are
10 demonstrated as a lattice of spheres. So if this were to
11 form a hydrate, you would see that as water molecules
12 contained within that lattice.

13 And having a hydrate changes the bioavailability
14 of a compound. It affects different issues of
15 manufacturability. So having a polymorph that's resistant
16 to hydration during manufacture is something that is
17 generally desirable, and it's a type of stability that is
18 influenced by polymorph.

19 I note there are no -- there are no data about
20 this type of stability in the patent.

21 Q. And here on slide 24, what is the stability you're
22 referring to?

23 A. So a second type of stability is that of chemical
24 stability. So if you have a molecule that either through
25 the action of light, what's called photochemical degradation

1 or through just thermal processes can fall apart, you know,
2 basically, it changes its molecular structure. This is a
3 type of chemical stabilization. This is something that
4 sometimes is related to shelf life of a material, because if
5 the active pharmaceutical ingredient is degrading, it no
6 longer will have its medicinal action, so stability of that
7 sort towards chemical degradation is something that is also
8 influenced by polymorph.

9 I did not see any data for chemical degradation in
10 the patent either.

11 Q. The next slide that you prepared, you have
12 thermodynamic stability. Can you please explain this?

13 A. So the third type of stability is thermodynamic
14 stability, and this basically says which polymorph is most
15 stable at a given temperature. And so here is an example
16 where there's a monoclinic lattice on the left and an
17 orthorhombic lattice on the right, just two different
18 arrangements, two different polymorphs of the same things,
19 and depending on the conditions of temperature and pressure,
20 the conversion may go left to right or right to left. So
21 this is another type of stability.

22 Q. And why would thermodynamic stability be important for
23 pharmaceuticals?

24 A. So thermodynamic stability is intimately related to
25 the concept of solubility, and so when a solid dosage is

1 taken, it dissolves in the body, and depending on which
2 solid form, which polymorph you're taking, it can affect the
3 rate of dissolution, and this, therefore, can affect the
4 rate of bioavailability.

5 In general, for that particular aspect of
6 thermodynamic stability, having a less stable form is more
7 favorable. It will lead to better dissolution behavior to
8 have a less stable form.

9 On the other hand, there is considerations with
10 manufacturing, and often you don't want your polymorphic
11 form to change during manufacture, and so this would suggest
12 to one to use the most stable polymorph for that reason.

13 So you see these two factors are somewhat in
14 conflict about what is the most desirable polymorph to
15 develop into a dosage.

16 Q. So did you prepare a slide to summarize, you know, all
17 these questions that you have about that disclosure of
18 utility?

19 A. Yes. I've broken out each part of the statement here.

20 So, first, the statement that "crystalline Form A
21 according to the invention has the same pharmacological
22 activity as Form B" is not a basis for utility, so this was
23 already -- that Form B was already there, and so this is not
24 new utility.

25 The stability, as we discussed, is not defined.

1 We don't know what type of stability we're talking about,
2 and if it's more stable under ambient conditions,
3 furthermore, we don't even know if that's advantageous
4 because of that tension between having a less stable form,
5 making it more soluble, or a more stable form sometimes
6 being more favorable for manufacture.

7 But I note in any case under ambient conditions we
8 don't see stability data for the chemical type of stability,
9 for the stability towards hydration. Nor do we see data for
10 the thermodynamic stability.

11 Q. So, Dr. Matzger, do you have an understanding of what
12 Plaintiffs claim is the utility disclosed in this patent?

13 A. I do. So Dr. Bernstein says that the '364 patent
14 discloses that Form A is thermodynamically more stable at
15 room temperature, so that third definition of stability we
16 talked about. And he also claims that this stability
17 relationship holds both at room temperature and at body
18 temperature.

19 Q. And I think you may have touched on this, but if true,
20 do you agree that this is a quality of utility?

21 A. Well, it's -- it's not really clear. I think that you
22 may want to have a less stable form for the potential
23 improvement in bioavailability, so it's not clearly a basis
24 for improvement. But it's also not demonstrated in the
25 patent.

1 Q. And so on thermodynamic stability, what kind of
2 information would you expect to see to learn about that?

3 A. So the most typical way to determine stability
4 relationships between forms is to look at solubility data,
5 and I've got a slide on that particular issue, so here is
6 just some background. So it just says "Solubility is an
7 important factor because the relative thermodynamic
8 stability of polymorphs and the direction of the
9 transformation between them are determined by the solubility
10 of polymorphs."

11 So solubility is the typical way to quantify the
12 energy difference between two forms.

13 There is no solubility data present in the patent.

14 Q. And for the record, you're reading from DTX 141, which
15 is in your binder, but can you also just tell us what 141
16 is?

17 A. So this is just an article by Kitamura that discusses
18 some of these issues of stability and transformation in
19 pharmaceutical polymorphs.

20 Q. So considering that, do you know what Dr. Bernstein
21 relies on for his opinion?

22 A. So my understanding is that his opinion comes from
23 Example 16, which is shown here, and also, this is data
24 about the conversion of one form to produce Form B from Form

25 A. So what they did in this experiment was, they heated

1 Form B and then they monitored the form during that heating,
2 and they observed that Form A converted to Form B from
3 between 40 to 50 degrees Celsius. And then they further
4 state that the result is reversible and that Form B changes
5 over into Form A at some lower temperature.

6 However, this lower temperature is not specified,
7 and it's critical for understanding the relationship between
8 the forms.

9 Q. And to be clear, I think you said Form B was heated.
10 Which form is heated in this experiment?

11 A. So -- okay. In the powder x ray experiment, they
12 produced Form B from Form A, so Form A converts to Form B
13 between 40 and 50 degrees.

14 Q. Thank you.

15 Now, is there anything else in the patent that
16 could inform you about this lower temperature?

17 A. So there is a discussion of the reverse conversion, so
18 producing crystalline Form A from Form B. And so the
19 description of that, it's in the specification, it's also as
20 shown here in Claim 17, and so if Form B is heated for a
21 time between 24 hours and 168 hours --

22 Q. Sorry. You said heated, or cooled?

23 A. Sorry -- is cooled for a time between 24 hours and 168
24 hours to a temperature of between minus four and minus 80
25 degrees Celsius, so minus four, that's below freezing, so if

1 you get that there, and then minus 80 is actually quite
2 cold, somewhere in there, and you hold it for this, you
3 know, over a day or more, then you can get conversion of
4 Form B to Form A.

5 Q. And have you prepared a demonstrative for us to kind
6 of explain what these two statements now lead you to
7 question?

8 A. Yes. So these are all the data we have about the
9 conversions, and so what I did is put that on a graph here
10 so we can see what we know about the transformations.

11 So we know that above 50 degrees that B is
12 definitely more stable. A converts to B. That's shown by
13 the powder x ray diffraction experiments.

14 Now, between 40 and 50 degrees, I have that kind
15 of hatched because we don't know exactly where in that range
16 the conversion occurs. They say it occurs between 40 and 50
17 degrees. But somewhere at least between 40 and 50 degrees,
18 B becomes the most stable form.

19 Now, on the other side, we know that A becomes the
20 more stable form because B converts to A. If we go to minus
21 four degrees C, so that's 25 degrees Fahrenheit, or below,
22 all the way down to minus 80, what this leaves us with,
23 though, and that's what I've boxed here, is this large area
24 of uncertainty where the patent is silent on what the
25 conversion is, and this encompasses a couple of very

1 important temperatures.

2 For example, room temperature, 22 degrees,
3 roughly, Celsius, 72 Fahrenheit, we don't know which -- from
4 the patent which form is more stable there.

5 It also doesn't discuss at body temperature what
6 occurs. This is important for knowing the relative
7 solubility relationship.

8 So the patent doesn't speak to these.

9 Q. And again, what kind of data could have explained this
10 information?

11 A. So let's see. The trial exhibit -- I think I have it
12 on the next slide --

13 Q. I believe you're -- yes, referring to DTX 928?

14 A. DTX, yes, 928.

15 So this is an example -- we talked about the
16 importance of solubility in determining relative stability
17 relationships. This is the type of data that one would
18 provide. This was a study that was conducted by SSCI. SSCI
19 is a contract crystallization group that's very expert in
20 doing these kinds of studies, as well as polymorph discovery
21 efforts, and so they had conducted solubility studies at
22 Grunenthal's direction to understand the relationships
23 between Form A and Form B.

24 I note these studies were conducted in 2002, a
25 couple of years before the priority date. But these data

1 were not included in the patent.

2 Q. Similarly, can you turn to DTX 1158?

3 And what is this document, Dr. Matzger?

4 A. So 1158 includes some solubility data. This was
5 collected at Grunenthal.

6 Q. And you're looking at -- let me just point out the
7 page here -- Bates ending in 74578, which I believe -- is
8 that a snippet of that page?

9 A. Yes, that is.

10 And so what's determined here is the solubility of
11 polymorph A and polymorph B in a couple of different
12 solutions. These are data that are collected at -- around
13 room temperature, so the results would be slightly
14 different. Actually, the solubilities we know from other
15 documents but not from the patent would be even more similar
16 in body temperature at 37 degrees.

17 Now, these data were not included in the patent,
18 but this was also collected about a year before that 2004
19 date that's of relevance for the '364.

20 Q. So based on the foregoing, do you have an ultimate
21 conclusion on the utility of the '364 patent?

22 A. Yes. I don't see demonstrated utility of the '364
23 patent.

24 Q. Thank you.

25 Okay. Let's move on to the next opinion you're

1 going to be offering today.

2 You are also here today to offer your opinions
3 about unclean hands.

4 A. Correct.

5 Q. And have you prepared a slide to summarize your
6 understanding of the legal standard?

7 A. Yes, and I will repeat my warning that I am definitely
8 not a lawyer, but this is my understanding of the unclean
9 hands. This is sort of my understanding in my own
10 interactions with the Patent Office.

11 So the Patent Office has to rely on statements
12 that are made by applicants and use that in figuring out if
13 they should be granting a patent, and so if there's
14 misconduct, misleading statements made to the Patent Office,
15 those can be grounds for making a patent unenforceable.

16 Q. Thank you.

17 So let's turn back to DTX 304, which is the '364
18 patent.

19 What did you want to call out for us here in this
20 patent?

21 A. So we're looking at the summary of the invention here.
22 So the claimed invention is a new form, Form A, termed Form
23 A, and importantly, this was different, and this becomes
24 important in the examiner's determination, that this is
25 different from Form B that is said to be obtained by Example

1 25 of the '737 patent. That's the 1994 date patent.

2 Q. And if we turn to the next slide you've prepared,
3 slide 40, you cited here DTX 1361, which is also in your
4 binder, but you've also prepared a snippet at page number
5 59017.

6 How is this significant to your opinion?

7 A. So this is a statement of allowability for the patent,
8 for the '364 patent, and it gives a bit of the basis, things
9 that the Patent Examiner relied on in granting that patent,
10 and it points to the figures throughout the specification
11 and relates those to the closest prior art, which is the
12 '737 patent. And so it's those pieces of information that
13 are used to draw the conclusion that the subject matter is
14 patentable.

15 Q. And for this issue, what analysis did you undertake to
16 arrive at your opinion?

17 A. So here, in contrast to the utility discussion that we
18 had, I looked beyond the '364 patent, I looked at internal
19 documents, and to understand more broadly what was known at
20 the time that this patent was filed.

21 Q. And, Dr. Matzger, you have several bases for your
22 opinion in this regard; correct?

23 A. Yes, I do.

24 Q. And what is your first basis?

25 A. So the first is -- I'll show a few examples from this

1 -- is that by 2001, well before the 2004 date, Grunenthal
2 knew that Form A was everywhere. This stuff was ubiquitous.
3 It kept cropping up all the time. Actually, the challenge
4 in many cases was to get Form B.

5 Q. Okay. Let's turn to DTX 1088 in your binder.

6 A. Okay.

7 Q. Okay? And, Dr. Matzger, have you prepared a slide
8 summarizing the relevant parts of this document for us?

9 A. Yes, I have.

10 Q. So here we have on slide 43 a snippet from this
11 document.

12 What did you consider significant from this
13 document?

14 A. So SSCI had been provided with Form A from Grunenthal,
15 and it was their goal to discover as many solid forms of
16 tapentadol hydrochloride as possible, and this is some of
17 the conclusions from their study. So they had found this
18 Form B, which was a high-temperature polymorph, but they
19 found that they were having trouble generating it in pure
20 form during their polymorph screening. In other words, it
21 was always contaminated with A when they tried to produce
22 it.

23 Q. And, Dr. Matzger, do you know of SSCI outside this
24 litigation.

25 A. Yes. They're a very rep -- they were probably one of

1 the first companies that really seriously did this business
2 of crystallization for hire, and so they developed quite a
3 lot of in-house expertise.

4 Q. Okay. And the next document we should turn to is
5 DTX 1087. I believe it should be the next tab right before
6 that.

7 And have you prepared a slide for us to summarize
8 what you considered pertinent about this document?

9 A. Yes. So this is additional information about studies
10 that were going on with SSCI under Grunenthal's direction,
11 and basically, again, they reiterate Form B, pure Form B
12 they hadn't isolated at this point. They explain that the
13 Form A is what they had received from Grunenthal.

14 And now we see something that's also highlighted
15 next that is the basis for what becomes Claim 16 that
16 we've --

17 Q. Claim 17? I'm sorry, is that what you're referring
18 to?

19 A. Example --

20 Q. Claim 17 or Example 16? Lots of numbers.

21 A. Sorry. Example 16, sorry, that becomes the basis for
22 Example 16. That's the powder x ray diffraction experiment.

23 And so you see they discuss here that they've
24 heated the material and that form -- they obtained Form B
25 through heating. However, they did x ray analysis of the

1 same sample the next day. Basically, this means it's
2 sitting under ambient conditions, you know, under this
3 condition, and that it converted back to Form A.

4 So here is a description, and this is not -- this
5 is absent from Example 16 in the patent where they just say
6 some lower temperature, they leave it ambiguous, but the
7 SSCI report says clearly that it just converts back to A
8 when it returns to room temperature.

9 Q. And what is the date of this document?

10 A. So this is 2001, so this is, you know, roughly three
11 years before the priority date of the '364 patent.

12 Q. Now, can you please turn to DTX 1075?

13 A. Yes. This is internal Grunenthal documents.

14 Q. And you prepared a slide to summarize the relevant
15 portions for us?

16 A. Yes, I have.

17 Q. And what did you find significant to your opinion?

18 A. So this just is a statement where they've been
19 synthesizing tapentadol hydrochloride and they find that the
20 product from the synthesis is Form A. This is the result
21 they were getting in-house. They were producing Form A by
22 synthesis.

23 Q. And I think one more document in the set. I'll have
24 you turn to DTX 1242.

25 A. Yes. So there are quite a few points in here. This

1 is Andreas Fischer's summary of polymorphism, again,
2 internal Grunenthal documents.

3 Q. And who do you understand Andreas Fischer to be?

4 A. He is one of the inventors on the patent.

5 Q. And what is the general date of this document?

6 A. So this is -- this is now 2005.

7 Q. And what on this page that you've blown up for us here
8 at 129619 Bates stamp did you consider significant to your
9 opinion?

10 A. So here, there are a few different things. So one is,
11 the solubility is discussed, and the comparable
12 bioavailability is discussed. Also, the issue is that
13 modification A is something they continue to be able to
14 produce reproducibly because it's, you know, the most stable
15 form and fairly easy to produce and stable. They talk about
16 some of the analysis, and then they discuss that they're
17 still not -- don't have a full understanding of Form B, that
18 they're seeing shifting in thermal events. So Form B,
19 again, paints a picture of Form B being a thing that's not
20 well understood, and Form A is the thing that they already
21 had a good understanding of.

22 Q. And now, Dr. Matzger, what is the second basis for
23 your opinion of unclear hands?

24 A. So I looked at the origin of various examples and
25 figures. Let's talk first about the figures in the patent.

1 So this describes a preparation of Form B, so it
2 claims that this was prepared according to Example 25 of
3 European Patent '475. That is equivalent, that Example 25,
4 to the '737 patent, the 1994 patent.

5 And so they say this is how they obtained
6 crystalline Form B, and that this is proven by powder x ray
7 diffraction. This is what they call B(1). Then Example 10,
8 they discuss the powder x ray diffraction pattern of B(1)m
9 and that's what appears in Figure 4.

10 Q. And moving on now to slide 49, what is this figure
11 here?

12 A. Okay. So this is Figure 4, so this is the one that
13 was just referred to, and this is the only unique pattern in
14 the -- of Form B in the patent, so there is also Figure 8,
15 but it's equivalent, it's just got labels on it, so really,
16 this is the origin of where they're saying they got their
17 powder pattern from for their Form B, the supposed prior art
18 form.

19 Q. So what is your issue with Figure 4 here?

20 A. So Figure 4, it turns out, did not come from the
21 product of Example 25 as represented to the Patent Office.

22 Q. And how do you know that?

23 A. So if we can take a look at the next slide, so the --
24 it was -- in looking at CEP1a, so looking at the lab
25 notebooks associated with the production of that and the

1 data that was disclosed, it was clear that this is the basis
2 for Figure 4 and the equivalent Figure 8 in the patent. So
3 that's the material that was used for the PXRD patent.

4 This was certainly not prepared by Example 25 of
5 the '475 patent, and, in fact, the Plaintiffs admitted so in
6 this response.

7 Q. And for the record here, you're citing to DTX 39,
8 which is in your binder, and DTX 146.

9 Can you refer to DTX 39 and let us know what that
10 is? We may be coming back to it a few times.

11 A. Okay. So DXT 39.

12 Q. It should be the first tab.

13 A. Right.

14 Okay. So these are deposition materials for
15 Struck. These are from the Struck deposition.

16 Q. Thank you.

17 So, Dr. Matzger, do you have an understand what
18 CEPM1a is?

19 A. Yes, I do. So I've reviewed the lab notes associated
20 with -- with that material.

21 So CEPM1a was made by a fairly unusual process,
22 which I'm going to illustrate here.

23 So when the crystals were grown -- when you grow
24 crystals, you have what's called the mother liquor. It's
25 kind of a funny name, but it's the fluid that's on top of

1 the crystals, and that is where the impurities become
2 concentrated. So the relatively pure material crystallizes
3 out, and then the impurities that are rejected from the
4 crystals reside in the mother liquor.

5 So what you typically do is, you filter the
6 material, you collect it, and it's shown here, on filter
7 paper, and then that's your pure material. And in this
8 case, the material on the filter paper is what is called
9 CEPM1.

10 Then CEPM1a is produced by removing the solvent
11 from the mother liquor, so concentrating down the impure
12 part of the sample to give the CEPM1a solid.

13 Q. And you said that you relied on several lab notebooks
14 and other documents in this case for this understanding.

15 If I turn now to slide 53, is this one of the
16 documents that you relied on for your opinion in this case?

17 A. Yes. So this shows the preparation of this material,
18 and it shows that CEPM1, those are the crystals that are
19 separated by filtration, and then CEPM1a, that's the
20 material that's obtained by evaporating the filtrate.

21 And it's I think important to note here that
22 CEPM1, this is Form A. You actually get Form A in that case
23 from the relatively pure material.

24 CEPM1a, which is concentrated in the impurities,
25 this becomes what they represent to be their Figure 4 of the

1 '364 patent.

2 Q. And for the record, this is DTX 1097, and the date on
3 that, can you let us know what the date is either by
4 onscreen or looking at the document?

5 A. Yes. So that's June 22nd, 2001, so again, well
6 obviously prior because this became the basis for figures
7 that were in the patent.

8 Q. And for the record, this is at Grunenthal production
9 GRT-NUC00063351.

10 Okay. Is there anything else that you'd like to
11 discuss about CEP1a?

12 A. Well, CEP1a had another -- there was a very
13 interesting observation with it, which is illustrated on the
14 next slide.

15 So when this material was initially made, it
16 showed Form A contaminating Form B, and my own analysis has
17 confirmed this, but this is actually from Grunenthal. They
18 put stars above the peaks that correspond to Form A.

19 So this material that became their representation
20 of Form B in the patent actually was initially found with
21 Form A in it. This was not disclosed to the Patent Office.

22 Q. And do you have the date of this document?

23 A. So this is September 12th, 2001.

24 Q. All right. Dr. Matzger, let's turn to your next basis
25 for unclean hands.

1 Can you explain a little bit about what you'll be
2 discussing here?

3 A. So I looked at a number of examples to try to
4 understand the origin of those experiments, and I'll just
5 show you one of those in particular, but this is fairly
6 typical. The examples are not supported by experiments that
7 were conducted.

8 Q. And here on slide 56, you have DTX 304, and what have
9 you highlighted for us?

10 A. So this is Example 2. This is the preparation of
11 Form A. And so it begins with the material that was -- is
12 used in this example, which they say is tapentadol
13 hydrochloride prepared according to Example 25 of the
14 European patent.

15 So this is what they represented is Form B, that
16 Example 25 of the European patent gives rise to Form B. So
17 they're saying here that they have started this experiment
18 with Form B.

19 Q. And what is your issue with this?

20 A. Well, it's not true. They didn't actually start with
21 Form B. So the basis of this experiment is shown here.
22 This was conducted by -- starting with Form A. So
23 essentially what they've done -- this is the material that
24 was given to SSCI, and you'll recall they were supplied with
25 Form A. So what the example basically involves is taking

1 Form A and converting it into Form A. And so this was
2 misrepresented to the Patent Office.

3 Q. So just for the record here, the top quote you have is
4 from DTX 39, which I believe we just looked at. That was
5 the deposition materials of Grunenthal's 30(b)(6) witness --

6 A. That's correct.

7 Q. -- Dr. Struck; correct?

8 A. That is correct.

9 Q. Okay. And below that are snippets from DTX 1001,
10 which is in your binder, but what is that document?

11 A. Okay. So 1001 is sort of an update, an internal
12 Grunenthal update from work that was going on in SSCI.

13 Q. And the pages that you've provided here are at 21094
14 and 21102. And can you just explain that one more time so
15 we don't get anything lost in translation here, how you
16 determined that it was Form A they started with?

17 A. So basically, this is what was disclosed in that 39
18 document. They gave the source of the examples. They said
19 it came from SSCI. SSCI received the material that they
20 determined to be Form A, and that's what they used in those
21 experiments that become the basis of this example.

22 Q. And is this issue limited to Example 2?

23 A. No, not at all.

24 Q. All right. Dr. Matzger, were you able to analyze any
25 study of tapentadol into your investigation of unclear

1 hands?

2 A. No, I was not.

3 Q. And why do you understand that to be?

4 A. Well, my understanding is, they were requested, but it
5 was claimed that no reference samples of Form B were
6 available.

7 Q. And would you have been able to analyze these crystal
8 forms if samples had been provided to you?

9 A. Yes, absolutely. My lab is well equipped to run
10 powder x ray diffraction. Even on extreme -- even if very
11 small sample quantities were supplied, I can get good powder
12 x ray diffraction patterns on those, but no material was
13 made available to me.

14 Q. And for the record here, on this slide 59, you've
15 cited DTX 39, again, Dr. Struck's deposition, and then
16 DTX 146, which is a piece of discovery in this litigation.

17 And do these documents confirm your understanding
18 of why no samples were available?

19 A. Yes.

20 Q. All right. Dr. Matzger, let's turn to the last part
21 of your opinion today.

22 As part of your work in this litigation, did you
23 consider the recreations done by Marita Mueller?

24 A. Yes, I did.

25 Q. And why did you consider them?

1 A. Okay. So -- and this is a bit of a subtle point. So
2 the document in 1994 that had supposedly produced Form B by
3 Example 25, that material was never tested, so there was no
4 data on what the polymorphic form was of that. So what
5 Grunenthal did was, they had Marita Mueller reproduce
6 Example 25 so that determination of the polymorphic form
7 could be done so that they could then say what the prior art
8 form was.

9 Q. And do you know how many recreations there were?

10 A. So I'm aware of four recreations that she conducted.

11 Q. And have you prepared some slides to demonstrate these
12 runs?

13 A. Yes. So I have a slide on each of these re-creations.
14 But before, there's a little bit of background in terms of
15 what I used to assess whether the results of her re-creation
16 were consistent with the result of Example 25 of the prior
17 art, the '737 patent.

18 So though we don't have powder x ray diffraction
19 from that, we do have some characterization of the product
20 of the '737 patent.

21 And so one issue is color. So in the most basic
22 organic chemistry lab course, we tell people that, you know,
23 your material, it should be white, and if it's off color,
24 you need to repurify it, you need to keep going. So color
25 in an otherwise colorless compound is an indicator of

1 impurities. And that's one of the things I considered,
2 because there was color data for the prior art material and
3 from the Mueller recreations.

4 Q. And what background do you have here for us?

5 A. So this discusses melting behavior, and the way I
6 represented this, this is differential scanning calorimetry,
7 so you're heating a sample and measuring heat flow.

8 And what this illustrates is two points, and these
9 will manifest no matter how you do the determination. If
10 you use a melting point apparatus or a differential scanning
11 calorimeter, you'll see the same thing. As you have a
12 fairly pure sample, you have a sharp melting point at a high
13 temperature, and then as impurities are introduced into the
14 sample, the melting point decreases and the melting
15 behavior, it broadens, it happens over a larger degree
16 range.

17 And so by looking at melting behavior, we can
18 conclude something about the purity of the sample.

19 Q. And if we turn now to slide 63, you titled this
20 Bu-322-1-1.

21 What information did you highlight for us here?

22 A. So this is the first attempted reproduction by Marita
23 Mueller. So what is shown here is, the material she made,
24 the color of this was mustard-colored solid. The documents
25 at Grunenthal show that the material obtained as the product

1 of Example 25 of the '737 patent was a white solid, and she
2 reports a melting point of 197 to 199 degrees Celsius.

3 The prior arts of the '737 patent said the melting
4 point was about 200 to 201, so a sharper and higher melting
5 point.

6 And that's consistent with a greater level of
7 impurities in the Mueller sample.

8 Q. And for the record, what you're pointing out is
9 DTX 1206?

10 A. That is correct.

11 Q. And DTX 1202.

12 If we turn now to slide 64, what have you prepared
13 a summary for us of?

14 A. So this also comes from that same lab notebook,
15 DTX 1202, but now this is the second attempt at recreating
16 Example 25.

17 In this case, she did not observe crystal
18 formation when following the procedure of Example 25, so she
19 deviated somewhat from the experiment to get crystals to
20 form.

21 When those crystals ultimately formed, they were
22 cream-colored and they had a very low melting point, so this
23 is almost 25 degrees lower than is expected, which for a
24 melting point is, you know, like a different compound,
25 almost. And so I guess seeing these results, no analysis

1 was done on the powder x ray diffraction of this material,
2 so we don't know what form she obtained.

3 Q. And if you can see there, what is the date of these --
4 sorry. Strike that.

5 What is the date of these experiments?

6 A. So this one is November 26, 2002.

7 Q. And now if we go on to your next slide that you
8 prepared for us regarding Bu-322-1-3, what would you like to
9 point out for us?

10 A. So this is then November 29th, 2002, and so this is
11 the third attempted recreation. The material now is beige
12 colored, again, not white, like the prior art. The melting
13 point is rather broad and lower than was reported for the
14 original material that forms the basis of Example 25.

15 Q. And did you analyze any other data in connection with
16 this run, Bu-322-1-3?

17 A. Yes, I did. I looked at the powder x ray diffraction
18 patterns that were provided.

19 Q. So have you prepared this slide, Bu-322-1-3, to
20 discuss today?

21 A. Yes. So this is just sort of a global view of the
22 pattern, and I'm just comparing it to Figure 1, Form A in
23 the patent just to illustrate that the signal to noise in
24 this pattern is very poor. So the one on the left is such
25 that you would not be able to determine even moderate levels

1 of Form B in this sample.

2 Q. And when you say "signal to noise," can you, you know,
3 maybe further explain that to us?

4 A. Yes, absolutely. So if you look at the -- and I --

5 Q. If you want to come forward --

6 MS. SHARKEY: Your Honor, I have a pointer.

7 THE COURT: That's fine, if you'd like to do that.

8 THE WITNESS: Okay.

9 (The witness stepped down.)

10 A. All right. So the noise level is essentially defined
11 by the width of this feature, so all of this -- these kind
12 of vast squiggles here are the noise level. And they're
13 present here as well, but you see their magnitude relative
14 to the height of the peaks is much smaller.

15 So that's what we mean by signal, this signal
16 height, to the noise level. So the signal height, to this
17 much smaller noise level.

18 So the signal to noise here is I'd say
19 reasonable, and the signal to noise here is quite poor.

20 Q. And why does that make it difficult to see forms in
21 this pattern?

22 A. Well, so, for example, if you were to see something
23 like this, is that enough, you know, signal, would that --
24 would you say that that's present or not? When it gets that
25 close to the noise, it gets harder to make those kinds of

1 assignments confidently. And the same would hold for if
2 there was, you know, a moderate level of Form A in here, it
3 would be difficult to detect.

4 MS. SHARKEY: Your Honor, is it okay if he stays
5 right here? We have a couple more slides like this.

6 THE COURT: Sure. That's fine.

7 MS. SHARKEY: Okay.

8 Q. And did you prepare a blowup of this pattern for us
9 today?

10 A. Yes. So I looked at a couple of regions of this
11 pattern. So now we've blown this up quite a bit. We're
12 only looking at five degrees of the pattern. So what's in
13 red here is identical to what you saw on the previous slide,
14 but now I've added, so it's the same as this, just blown up
15 in this region.

16 But what I've added on here is these blue boxes
17 that illustrate the expected positions from the '364 patent.
18 So at each position where a peak was reported in the table
19 of the '364 patent, I've put a box with a width of .2
20 degrees at the top.

21 Q. And what form is that in blue?

22 A. So that is Form B in blue. So we're comparing Form B,
23 the peaks of Form B in that table to Mueller's recreation,
24 which was interpreted to lead to Form B.

25 Q. And what have you pointed out for us here?

1 A. So -- well, first, just globally, if you look at over
2 all, the pattern has kind of shifted from where the peaks
3 are expected to be in the table. So this is not a very
4 accurate representation if this is, in fact, Form B.

5 But also, there are a number of peaks that are
6 unaccounted for. So if you look at these signs and -- like
7 this peak here, here's a peak that is not expected for Form
8 B.

9 And there's another slide that shows you
10 similarly.

11 So these peaks have significant enough signal to
12 noise that they are real, but they're not found in the
13 Form B table.

14 Q. And for the record here, we're on slide 67, and you
15 were first here pointing at a peak at around 17.6?

16 A. That's correct, about 17.6.

17 Q. And then on slide 68, you were pointing at a peak
18 around 24.4; is that correct?

19 A. Correct.

20 Q. And now can we talk about this last, fourth run by
21 Mueller?

22 A. Yes. So this was the final one I analyzed.

23 Q. And what did you want to highlight for us here from
24 DTX 1034?

25 A. So now the solid is described as cream-colored. The

1 melting point again is somewhat broader than was found in
2 the result of Example 25.

3 Now, this is, by the way, I'll note, a much later
4 recreation, so this is now 2009. This is after, well after
5 the priority date of the patent.

6 Q. And did you analyze any data in connection with this
7 run?

8 A. Yes. So now this one has a powder x ray diffraction
9 pattern that's of fairly high quality, and so this one can
10 be analyzed in a bit more detail than those very noisy ones.

11 Now, I want to point out there is still noise
12 here, it's just very low. It's, you know, very low in the
13 baseline here. So this is -- the signal to noise here is
14 fairly good.

15 So there are three patterns that are overlaid
16 here, okay? And those three patterns are a standard of
17 Form A, that's in green, a standard of Form B that's in red,
18 and then the Mueller fourth recreation, that's in blue.

19 Q. And was this something that you prepared?

20 A. No, this was -- this was provided by Grunenthal.

21 Q. And what are you pointing out for us here?

22 A. So the things to look at -- there are a couple things.
23 So one is, if you look at green, this is Form A, and then
24 you look at red, which is the Form B standard, you see that
25 it's actually contaminated by form -- by the other forms.

1 So here, there's a peak under here that's evident, there's a
2 peek here that's evident. So even their standard is not
3 free of Form A in this case.

4 But I think even more important is to look at the
5 differences between their standard pattern of Form B and the
6 material that Mueller created.

7 So if you look at blue and red here, they overlay
8 almost perfectly, so there's very good agreement between
9 these positions. But then as we go over, you see blue and
10 red no longer overlay. Then as we go over again, they
11 overlay well, they overlay well, and they don't overlay.

12 This sort of behavior is a telltale sign of
13 impurity incorporation. So what happens is, the impurities
14 go into the lattice and they expand it selectively in some
15 dimensions and you get shifting of just some of the peaks of
16 the powder x ray diffraction.

17 Q. Thank you. And for the record, the peaks that you
18 were pointing to were at 20.2 and 22.0; is that correct?

19 A. Those are the peaks that are shifted, and then at
20 about 19.6, that one's not shifted, and at about 21, there's
21 not much shifting.

22 Q. And for the record, this is at DTX 1317.

23 A. Correct.

24 Q. So, thank you, Dr. Matzger. I think you could just
25 conclude right now. What is your ultimate opinion on these

1 Mueller recreations?

2 A. So these are not faithful reproductions. They don't
3 provide material with the same properties as that of Example
4 25, and so they're not a basis to show that Form B alone was
5 created.

6 MS. SHARKEY: Thank you. I think you can return
7 to your seat.

8 I have no further questions.

9 THE COURT: Thank you very much.

10 You can begin your cross.

11 MR. GLANDORF: We'll hand out the binders at this
12 point, Your Honor.

13 THE COURT: Sounds good. Thank you.

14 MR. GLANDORF: Your Honor, I think I have about an
15 hour. I'm okay to power through it.

16 THE COURT: Do you want to take our lunch break
17 instead now? It's up to you.

18 MR. GLANDORF: That would be fine. We can take a
19 quick one, probably.

20 THE COURT: Do you want to do that, or do you want
21 to get started and then take your break?

22 MR. GLANDORF: Either is fine with me. Let's take
23 a lunch break now and, we'll continue after a short break.

24 THE COURT: All right. Let's do that. So we'll
25 break for 45 minutes? Yes?

1 I'll give the instruction, but is there any other
2 issue? I know you popped up rather quickly.

3 MR. SCHULER: I just wanted to verify that we can
4 actually take a break and see if lunch is here.

5 MS. WIGGINS: We're not sure --

6 THE COURT: Oh, whether the lunch has arrived?

7 (Off the record discussion)

8 THE COURT: Why don't we do this: Let's start a
9 little bit until our deputy comes back and lets us know.

10 MR. GLANDORF: That will be fine.

11 THE COURT: All right.

12 MR. GLANDORF: May I approach with the --

13 THE COURT: Yes, certainly.

14 Any issues with respect to the exhibits?

15 MS. SHARKEY: Not at this time.

16 THE COURT: Okay. Are there any demonstratives?

17 MR. GLANDORF: No.

18 THE COURT: Very well. Let's begin.

19 CROSS-EXAMINATION

20 BY MR. GLANDORF:

21 Q. Good afternoon, Dr. Matzger.

22 A. Good afternoon.

23 Q. My name is David Glandorf, I'm from Gibson Dunn, and
24 I'm representing Depomed today.

25 Were you here in the courtroom for Dr. Steed's

1 testimony?

2 A. No, I was not. I was here this morning.

3 Q. You were here for the cross-examination; is that
4 right?

5 A. That is right.

6 Q. Now, Doctor, in your opinion, is Form A of tapentadol
7 hydrochloride the more stable form?

8 A. Yes, of pure tapentadol hydrochloride, I think there's
9 little question that it's the more stable form.

10 Q. And it's more stable at room temperature?

11 A. Yes.

12 Q. I think you testified to this, but let me just
13 confirm, what is room temperature in your mind?

14 A. Around 22 degrees Celsius.

15 Q. And at that temperature, is Form B unstable or is it
16 metastable?

17 A. So it is certainly metastable, and it appears also to
18 be unstable when in pure form.

19 Q. Could you tell us --

20 THE COURT: I'm sorry. Could you have the witness
21 explain what metastable is?

22 MR. GLANDORF: That was my question.

23 A. Oh. Sorry. Yes.

24 So metastable, at one temperature and pressure,
25 you typically can only have one form that's the most stable,

1 so one form that's the thermodynamically most stable. So
2 any other form is metastable in that sense. It's motivated
3 to convert to that other form, but then the issue is, will
4 it convert or not.

5 THE COURT: Okay. You can ask him your questions
6 again in terms of the temperature so we can get a clear
7 answer. Thank you.

8 MR. GLANDORF: Do you want me to ask the questions
9 again?

10 THE COURT: Yes, at 22 degrees Celsius --

11 Q. Would you describe Form B as metastable or unstable?

12 A. So pure Form B is metastable under those conditions,
13 and I would say it's also unstable.

14 Q. Let's talk about your criticisms of Ms. Mueller's
15 recreation. Can we do that?

16 A. Sure.

17 Q. And you testified to how many recreations by
18 Ms. Mueller?

19 A. I discussed four recreations, three where the product
20 was characterized.

21 Q. And of those four, the four that you mentioned, do you
22 know how many Grunenthal relied on to obtain the '364
23 patent?

24 A. So I don't know exactly. I would assume they didn't
25 rely on the 2009 example because that was later.

1 Q. That leaves the three 2002 --

2 A. Right. So one of those they never tested, so I guess
3 they didn't rely on that one, and I don't know of the other
4 two how many of those they relied on.

5 Q. But you criticized, like, for example, the 2009
6 recreation even though Grunenthal didn't rely on it to
7 obtain the patent; is that right?

8 A. Yes.

9 Q. Okay. And the same for the second of the 2002
10 recreations? You criticized it even though it wasn't relied
11 on, to your knowledge.

12 A. Yes.

13 Q. Now, you have not concluded that Form A was present in
14 Marita Mueller's first batch, which, if I call it 322-1-1,
15 are you okay with that?

16 A. That's fine.

17 Q. You did not conclude that Form A was present in Marita
18 Mueller's 322-1-1 batch; is that right?

19 A. No, I concluded that it may have been present.

20 Q. You didn't definitively conclude that it was present;
21 is that right?

22 A. I did not definitively conclude that it was present or
23 absent.

24 Q. Now, you were discussing impurities throughout today.
25 Is it your opinion that the only way to have stable Form B

1 room temperature is to have impurities?

2 A. So it's the only way I'm aware of it being stabilized
3 when it's -- when it's crystallized from solution.

4 Q. And what are you basing that opinion on?

5 A. Well, CEPMLa is a good example, so you have CEPML,
6 which is Form A, and then you take the mother liquor, the
7 impurities from that, and you are able to obtain Form B.

8 Q. So you know about -- you're referring specifically to
9 the CEPMLa example; is that right?

10 A. Well, and CEPML, the crystals that were harvested
11 prior to concentrating the mother liquor.

12 Q. I see. So those two samples, when you're
13 distinguishing them, did that provide you with that opinion?
14 Is that correct?

15 A. So they helped to inform my opinion, but I think there
16 are other examples as well.

17 Q. Okay.

18 MR. GLANDORF: Rob, can we pull up his slide deck?
19 Let's go to slide 60, if we could.

20 Do you have the slide deck from Defendants?

21 (Off the record discussion)

22 MR. GLANDORF: I believe your slide deck went up
23 to 70, is that -- 71? Does that sound right?

24 Q. All right. We will get that figured out in short
25 order. Let's just talk generally about it, though.

1 When you walked through your criticisms of
2 Ms. Mueller, all of your criticisms of Ms. Mueller were
3 focused on impurity; is that right?

4 A. I believe that's correct.

5 Q. And then your final conclusion here, I'll read it for
6 you, I don't think you have your demonstratives in front of
7 you here, but I'll read it: "These recreations are not
8 faithful and do not provide proof that Example 25 created
9 Form B alone."

10 Do you recall that conclusion?

11 A. Yes.

12 Q. So that conclusion is based on your description of the
13 impurities throughout Ms. Mueller's recreation; is that
14 right?

15 A. It's a comparison of the properties as described by
16 color and melting point relative to what had been reported
17 as the product of Example 25.

18 Q. But the color and the melting point in your mind,
19 those are evidence of impurities; isn't that -- wasn't that
20 your testimony today?

21 A. Those are evidence of impurities, yes.

22 Q. I guess my question is, it seems like we're missing a
23 step here in the conclusion. How is it that the fact there
24 are impurities in Ms. Mueller's samples lead you to the
25 conclusion that her recreations were not faithful

1 recreations?

2 A. Okay. So the faithful recreation should produce the
3 same product of Example 25 so that --

4 Q. Are you testifying, then, that Ms. Mueller did not
5 create tapentadol hydrochloride?

6 A. No. I am testifying that she did not produce it in
7 the same -- to make the same material that is the product of
8 Example 25, which is the relevant thing because that's
9 what's being used to tell the Patent Office what the product
10 of Example 25 is.

11 Q. Okay. Well, let's unpack that a little bit.

12 You agree that she created tapentadol
13 hydrochloride; is that right?

14 A. Yes, I believe she did.

15 Q. And when you say there are differences compared with
16 what her recreation made and what the prior art made, what
17 do you mean by that?

18 A. So there was data for the product from Example 25 that
19 is the basis of the '737 patent. It's comparing the data --
20 though they don't have powder x ray diffraction, so we can't
21 compare that, but we can compare the melting point and the
22 color.

23 Q. The melting point and the color. And what is the
24 color that is reported for Example 25 in the prior art?

25 A. I believe it's white.

1 Q. And what are you basing that on?

2 A. So it's an internal Grunenthal document, I believe.

3 Q. Is it a lab notebook? Did you present that lab
4 notebook here today? Did you present that -- the color of
5 the prior art today to the Court?

6 A. Did I discuss the -- yes, I did discuss the color of
7 the prior art.

8 Q. You did discuss the color. Did you provide for the
9 Court the basis, the evidentiary basis for that, the color?

10 A. I don't think it was in -- I don't think it was in the
11 documents.

12 Q. Well, let's discuss this.

13 Some of the colors of Ms. Mueller's were off
14 white; is that right?

15 A. Well, there was -- there was mustard, there was beige,
16 there was -- I think one other color, I'd say.

17 Q. A variety of colors; is that fair?

18 A. A variety of colors. Not a rainbow, but a variety of
19 colors, yes.

20 (Laughter)

21 Q. Fine. Fine with me. We'll talk about the variety of
22 colors.

23 My question here is, where are you drawing the
24 line? What color is okay for you? If it was off white,
25 would that have been a faithful recreation?

1 A. Well, I would expect it to be as the -- I mean, in my
2 own experience, when you synthesize something, you expect it
3 to be the same color as the procedure you're following, so
4 if the procedure says it's white, and if I get something
5 that's off white or mustard, generally it means I'm in need
6 of additional purification steps or to rerun the procedure.

7 Q. Now, this is not a spectroscopic evaluation of color;
8 is that right?

9 A. Of course it is.

10 Q. It's a qualitative measurement, though; isn't that
11 right?

12 A. Yes.

13 Q. It's a human understanding of what the color is; is
14 that fair?

15 A. Yes.

16 Q. It's possible to do it in an automated fashion and
17 compare it quantitatively; isn't that right?

18 A. It's actually not so easy on solids as you might
19 imagine. It can -- yes, it can be done.

20 Q. It's possible.

21 A. Yes, it's possible.

22 Q. Now, you'd agree that all chemical samples contain
23 impurities; correct?

24 A. Essentially, yes.

25 Q. And, in fact, you would expect that a person

1 performing Example 25 -- well, let's step back for a minute.

2 You understand Example 25, when I say Example 25,
3 I'm referring to Example 25 of the prior art of the '737
4 patent?

5 A. I do understand that, yes.

6 Q. And it's your understanding is that example, Example
7 25 of the '737 patent is the prior art here. You understand
8 that term?

9 I'll step back with the term. Let's not use that.

10 Let's go back to Example 25, though.

11 You would expect that a person of ordinary skill
12 performing Example 25 would get impurities; correct?

13 A. Correct.

14 Q. And yet you're drawing a line; at some point, the
15 impurities are, in your opinion, high enough that it no
16 longer represents a faithful recreation; isn't that true?

17 A. Yes, that's true.

18 Q. And what is that line, then, Dr. Matzger?

19 A. So when it doesn't share the color with the product,
20 and when it doesn't share the melting point and melting
21 range of the product.

22 Q. And so again, when you say color, you're relying on
23 the qualitative interpretation of the person in the lab; is
24 that right?

25 A. Yes.

1 Q. Let's talk about the melting point.

2 Melting point is a number; correct?

3 A. Well, more properly, it's ideally a range of numbers.

4 Q. It's a range.

5 Now, how close do the melting points have to be
6 before you, Dr. Matzger, would confirm that this is a
7 faithful reproduction?

8 A. So we have two things that we can look at here. So
9 one is the melting range, so sort of the breadth between the
10 low and the high number, and the other is the melting point.
11 So we can look at both of those in considering that.

12 Q. Well, let's look at them both, then. Let's look at
13 them one at a time.

14 My question to you is, how close does it have to
15 be? Where is your dividing line so that you can come in
16 here and determine whether or not this is a faithful
17 reproduction?

18 A. So I don't think I've got a firm answer for you on
19 what the dividing line is. When you have something that
20 melts five degrees lower than something else, this is
21 clearly quite significant. When the melting range sort of
22 doubles in broadness going from one degree to two degrees,
23 this also is -- usually means there's significant impurities
24 in the sample.

25 Q. But you don't have a line, you don't have a dividing

1 line. It's just that you looked at these melting point
2 differences and you were comfortable with your conclusion
3 here that they're not faithful reproductions. Is that true?

4 A. Yes, that's true.

5 Q. I first asked you when we talked on this topic whether
6 impurities stabilize B, and your testimony was that they do;
7 is that right?

8 A. Yes, there are certain impurities that stabilize B.

9 Q. And so --

10 A. Something -- although I want to clarify something,
11 because I think there's some confusion about this.

12 It's -- the question is, are you stabilizing
13 something with the powder x ray diffraction of Form B or
14 substantially similar to Form B, or is it Form B in the
15 sense of tapentadol hydrochloride, you know, pure in form,
16 in Form B, and this is where things can get a little bit
17 more complicated, as I illustrated with that last powder Ray
18 diffraction pattern I showed you.

19 Q. Let me make sure I understand what you're saying here.
20 You're saying that even though the x ray powder diffraction
21 pattern matches the standard for Form B, you won't go
22 forward and conclude that Form B is actually the crystal
23 form that's present?

24 A. Yes, so that doesn't tell you if it's pure tapentadol
25 hydrochloride Form B.

1 Q. Well, when you say "pure," are you talking about
2 chemical purity?

3 A. Yes, chemical purity.

4 Q. You're saying that even though the x ray powder
5 diffraction, the pattern indicates that we have Form B, what
6 you're trying to explain to me here, the qualification
7 you're making is that still may have impurities in it? Is
8 that your statement?

9 A. If it looks similar to Form B, it still does have
10 impurities in it, yes.

11 Q. And isn't that true also for if you had a sample with
12 an x ray pattern of Form A?

13 A. Yes, it's just in this case it seems like the impurity
14 incorporation into Form B is more substantial as shown by
15 the shifts in some of the powder x ray diffraction patterns
16 and it's substantial in effecting the conversion from Form B
17 to Form A as has been shown by the numerous experiments in
18 this case.

19 Q. But you didn't show any analyses, any close-up
20 analyses of a Form A sample today; isn't that right?

21 A. I just showed -- well, there was a close-up analysis
22 of the Form A -- yes, the last slide had a close-up of
23 Form A standard on it.

24 Q. Well, it had the Form A standard and the Form B
25 standard, but the only sample you looked at was Marita

1 Mueller's. You didn't compare those standards to a sample
2 that happened to be Form A; isn't that true?

3 A. That's correct, I didn't do any overlays for this of
4 that nature.

5 Q. Now, does the patent state that there is any advantage
6 of Form A over Form B?

7 A. I would have to look at the statement. Again, I think
8 it uses the term advantageous when comparing the forms.

9 Q. We can look at it. Shall we turn to '364 in your
10 binder? Plaintiffs' Exhibit 304 -- Defendants' Exhibit 304.

11 It's not in my binder, it's in your binder.

12 A. Oh, okay.

13 Okay. So --

14 Q. Now, you quoted from a section, I believe it's in
15 Column 4, about Row 13 or so. Does that look like the
16 paragraph?

17 A. Okay. So crystalline Form A according to the
18 invention has the same pharmacological activity as Form B,
19 which I understand not to be utility, but is more stable
20 under ambient conditions. So then it goes on to say "It can
21 advantageously be used as active ingredient in
22 pharmaceutical compositions.

23 Q. So I'll ask my question again. Does the patent state
24 that Form A has an advantage over Form B?

25 A. So it -- it says it can be advantageously used in --

1 as the active ingredient in pharmaceutical compositions. I
2 don't see a basis for this statement in the -- in the
3 patent.

4 Q. Well, do you understand the basis for that statement
5 to be the second half of the sentence prior to it, that it
6 is more stable under ambient conditions?

7 A. No, I don't, because sometimes it's desirable to have
8 something that's less stable under ambient conditions so it
9 will dissolve better. So, no, I don't understand how those
10 are connected, in addition to the ambiguity about what
11 stability means in this case.

12 Q. So let's go into your first comment there. You
13 testified about this, I think, that when it comes to
14 thermodynamic stability, it may be an advantage in some
15 situations, it may not be an advantage in other situations;
16 is that fair?

17 A. That's correct.

18 Q. And how do you as a person of skill in the art, how
19 would you decide whether to use the more thermodynamically
20 stable polymorph form or the less thermodynamically stable?

21 A. Well, I think it's the kind of thing one -- one tests,
22 because it can be -- it can be very complicated, because you
23 can get form conversions in vivo, and it's -- it's hard to
24 predict, let's say, until you've handled the material and
25 you know how it behaves during manufacture and how it

1 behaves during dosage. So that's why these things, you
2 know, are done.

3 Q. So you're aware, I assume, of some pharmaceutical
4 formulations where they have chosen to formulate and to
5 produce the more thermodynamically stable form?

6 A. The more thermodynamically stable form? Yes, sure.

7 Q. But there are also situations where they have decided
8 to go with the less thermodynamically stable form; is that
9 correct?

10 A. That's correct.

11 Q. Now, is it your understanding that in order to
12 establish utility, the patent must establish that Form A is
13 superior to Form B?

14 A. No, I don't think that that's the bar.

15 Q. Do you have an understanding of whether Form A
16 tapentadol hydrochloride is useful as an analgesic?

17 A. I have a general understanding that that's correct.

18 MR. GLANDORF: Rob, do we have those slides?

19 Okay. Before we get to that --

20 THE COURT: I was about to say, also, whenever
21 you're ready to break, I think the lunch is actually here.

22 MR. GLANDORF: Just two more questions.

23 THE COURT: You can go as long as you want, but
24 we're in good shape.

25 Q. Let's go to Example 16 if we could. Do you recall

1 testifying about Example 16?

2 A. I do.

3 Q. You have it in front of you there?

4 A. Right here.

5 Q. All right. You knew it.

6 Now, what's being discussed here is the conversion
7 from one form to the other; is that right?

8 A. Correct.

9 Q. And in this case, we are converting from Form A to
10 Form B; is that right?

11 You can look.

12 A. Well, it discusses conversions actually in both
13 directions.

14 Q. Okay. That's correct, right? And the first
15 conversion it discusses is one at -- that happens within a
16 temperature range of 40 to 50, and which conversion is that?

17 A. Okay. So that is the conversion of Form A to Form B.

18 Q. And does this data on the conversion from Form A to
19 Form B at 40 to 50 degrees provide you with some
20 understanding of the relative thermodynamic stability in
21 that temperature range?

22 A. So it doesn't tell you exactly where B becomes more
23 stable, but it tells you that it's somewhere that above 40
24 to 50 degrees or maybe within that range, we don't quite
25 know, that B is more stable than A.

1 Q. And this difference in stability, is that the kind of
2 data you would expect to see to establish utility?

3 A. No, because there's ambiguity with that. So let's say
4 there was a very sharp conversion at 50 degrees, and it
5 converts all the way from A to B. That doesn't tell you
6 that 50 degrees is the temperature at which the stability
7 relationship changes. So you still don't know about that
8 fundamental stability relationship at that temperature. All
9 you can say is, well, apparently, at that temperature, at 50
10 degrees, B is more stable.

11 Q. Okay. So let me make sure I understand. Let's go
12 down now, let's say if it was cooling, and it measured a
13 conversion from B back to A at 20 degrees.

14 A. Okay.

15 Q. Does that indicate to you the thermodynamic
16 relationship between the two forms at that temperature?

17 A. So you would note that at 20 degrees, A is more stable
18 than B, but you would not know at what temperature the
19 stability relationship changed.

20 Q. And just so I understand, when you talked about the
21 utility information of the patent, your testimony was that
22 there was no data on utility; is that right?

23 A. So there is stated utility, but I don't find it
24 supported by anything in the patent.

25 Q. And that's because, as you just discussed, there is

1 too much ambiguity here in Example 16; is that right?

2 A. Well, I haven't only considered Example 16, but
3 Example 16 certainly is ambiguous, and it doesn't tell you
4 where the transition temperature is in terms of the change
5 in stability relationship.

6 Q. So there's data --

7 A. Thermodynamic stability relationship.

8 Q. So there is data, you wanted more data here; is that
9 right? Is that fair?

10 A. I don't want anything. I just don't know what -- I
11 just can't find support for the statement about stability of
12 any sort at ambient temperature --

13 Q. All right.

14 A. -- pressure --

15 Q. Let me ask my question. I understand. Your desires
16 are not at issue here.

17 A. Right.

18 Q. When it comes to establishing utility, to establish
19 utility in this patent, you would have required more data on
20 the thermodynamic relationship; is that fair?

21 A. No. It depends on what they claimed the utility to
22 be. So that's what they claim the utility to be, so that's
23 what I would expect to see evidence for. If they claimed
24 that it had a particular morphology that was wonderful for
25 pressing into pharmaceutical tablets, I'd expect to see

1 evidence of that. You just -- whatever the utility is, I
2 would expect them to provide substantiation for that
3 utility.

4 MR. GLANDORF: Let's take our break here, Judge,
5 if that's all right.

6 THE COURT: That's fine. Yes.

7 We'll go to lunch. We'll take a 45-minute break.

8 Does that sound good?

9 All right. Forty-five minutes, back here.

10 The witness is released off the witness stand, but
11 again, I remind you as I remind all witnesses that you are
12 under oath and you are not to discuss your testimony with
13 counsel. All right?

14 THE WITNESS: Okay.

15 THE COURT: Thank you very much. We'll see you in
16 45 minutes.

17 THE COURT CLERK: All rise.

18 (Luncheon recess taken)

19

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1 A F T E R N O O N S E S S I O N

2 THE COURT CLERK: All rise.

3 THE COURT: Hello, everyone. Have a seat.

4 Let's have our witness return to the stand.

5 (The witness resumed the stand.)

6 THE COURT: And we may continue with the cross.

7 Sir, I remind you that you remain under oath.

8 Thank you.

9 THE COURT: Let's begin.

10 MR. GLANDORF: Okay.

11 We did add one document here, Your Honor, which is
12 the deposition testimony, and I think we have some copies
13 for the witness and for the Court as well.

14 THE COURT: Sounds fine. You may pass it up.

15 Any issue with that?

16 MS. SHARKEY: No, Your Honor.

17 THE COURT: Thank you.

18 MR. GLANDORF: May I approach?

19 THE COURT: Yes.

20 THE COURT CLERK: Are these the same?

21 MR. GLANDORF: They are.

22 THE COURT: Is it how they're copied?

23 MR. GLANDORF: I believe it's how it's copied.

24 One is four to a page.

25

1 CROSS-EXAMINATION (CONTINUED)

2 BY MR. GLANDORF:

3 Q. Dr. Matzger, we were discussing before the lunch break
4 the standard that you had applied for utility. Do you
5 recall that?

6 A. Yes.

7 Q. And I asked you if under your understanding of utility
8 whether it was necessary for Form A to be shown materially
9 better than the prior art. Do you recall that?

10 A. Yes.

11 Q. And do you recall what your answer was?

12 A. That's not my understanding of what the bar is for
13 utility.

14 Q. Well, let's go to your deposition transcript, then,
15 and I think this question came up.

16 MR. GLANDORF: Rob, do you have the deposition
17 transcript ready?

18 Q. Let's go to 238, lines 10 through 14.

19 THE COURT: Hold on one second. We're just going
20 to make it a little bit easier to read this.

21 MR. GLANDORF: That's better.

22 THE COURT: Okay.

23 Q. So at your deposition, you were asked:

24 "So it's your understanding that to satisfy the
25 utility requirement, the '364 patent must show that Form A

1 has a use that is materially different from the prior art,
2 correct?"

3 And your answer was "Yes."

4 Did I read that correctly, Dr. Matzger?

5 A. Yes.

6 Q. And I want to go back to one other thing. Let's just
7 talk real quickly once more about Marita Mueller and your
8 criticism there.

9 You showed the pattern for Marita Mueller's
10 resynthesis, 322- -- find it here -- -1-3. Do you recall
11 that?

12 A. Yes.

13 MR. GLANDORF: Let's go ahead and pull that up,

14 Rob. That is 566.

15 Q. You recall this slide, Dr. Matzger?

16 A. Yes, I do.

17 Q. And your testimony here was that Bu-322-1-3 was noisy;
18 is that correct?

19 A. That is correct.

20 Q. Did you also look for the --

21 THE COURT: Just one second. What slide number is
22 that?

23 MR. GLANDORF: It doesn't have a page number, the
24 version I have, Judge, but it's 66.

25 MS. SHARKEY: Yes, it look like the page number

1 didn't make it on the slide.

2 THE COURT: Page 66. Thank you.

3 Q. Did you also look at the XRPD pattern for Bu-322-1-1?

4 A. Yes, I did. It's not included in this presentation,
5 but it's in my expert report.

6 Q. And do you recall that that pattern was considerably
7 less noisy than 1-3?

8 A. It was less noisy. As I recall, it sort of was
9 intermediate between what we see here in Figure 1 and what
10 we see in Bu-322-1-3.

11 Q. And Figure 1 is from the patent; is that right?

12 A. Correct.

13 Q. And when you're presenting representative patterns in
14 patents or in publications, would a person of ordinary skill
15 choose a pattern that was -- that had strong signal to noise
16 in your opinion?

17 A. I mean, generally, it's desirable to have good signal
18 to noise if your purpose is to detect a low level of a
19 component within a pattern.

20 Q. And you also discussed that Marita Mueller's
21 reproductions may have suffered from impurities. Do you
22 recall that testimony?

23 A. Yes.

24 Q. And I just want to confirm, if we were to look at
25 Example 25 of the '737 patent, we won't find any purity

1 requirements there; is that right?

2 A. I'm -- I'm not sure. I don't believe so, but I -- you
3 would have to direct me to it.

4 Q. Let's go ahead and look at it, then. Let's get out
5 the '737 patent.

6 This is Defendants' Exhibit 752, and then Example
7 25 should be around Column 20 or so.

8 A. Do I have 752 in your folder, or --

9 Q. Not in our folder. I believe it should be in their
10 folder. It should be in your folder from the direct this
11 morning.

12 A. 752?

13 THE COURT: You know what? I think he has a
14 different number. I'm trying to find it as well.

15 MR. GLANDORF: All right. One moment. Let me
16 find it.

17 Q. Do you have Dr. Steed's binder available to you?

18 It's not there? Okay.

19 THE COURT: We should have one.

20 Jackie, we need Dr. Steed's.

21 You're looking for the --

22 MR. GLANDORF: I'm sure we can find it, Your
23 Honor.

24 THE COURT: We have a pile from our witnesses
25 here. If you want to take a look, you could probably find

1 it.

2 THE COURT CLERK: Well, it's not here. Somebody
3 cleaned it up before I came up here before.

4 THE COURT: The cross?

5 THE COURT CLERK: Do you need the cross notebook?
6 (Binders were provided to counsel.)

7 MR. GLANDORF: May I approach?

8 A. 752? Yes.

9 MR. GLANDORF: Okay.

10 Thank you, Mr. Schuler.

11 THE COURT: Thank you.

12 Q. You do have Defendants' Exhibit 752 in front of you
13 now, Dr. Matzger?

14 A. Yes.

15 Q. And could you turn to column 20 and find Example 25?

16 A. Yes, I'm there.

17 Q. Do you see any purity requirement here in Example 25?

18 A. What do you mean by a purity requirement?

19 Q. Do you see any minimum or any -- I'm sorry, any
20 maximum percentages in terms of purity?

21 A. No.

22 Q. Do you see any particular impurities identified?

23 A. No.

24 Q. Is there a color identified here for the product of
25 Example 25?

1 A. No.

2 Q. Now, you do not consider Ms. Mueller's reproductions
3 to be faithful reproductions; is that right?

4 A. That is correct.

5 Q. Is it your testimony that it would not have been
6 possible for Grunenthal to consider those reproductions they
7 paid for as reproductions of Example 25?

8 A. So, I mean, legally, I don't know, but I don't think
9 you'd want to rely on something -- so what they were trying
10 to do was figure out what was the solid form resulting from
11 practicing Example 25 of the '737 patent, so I would think
12 they would want the most accurate depiction of that. So
13 since there were several problems in those reproductions, I
14 think it would be improper for them to rely on them for --
15 for anything.

16 Q. Let's turn to some of your arguments on unclean hands.
17 Do you recall testifying about the destruction of
18 Grunenthal samples?

19 A. Yes, I -- well, I discussed the inability for me to
20 get Grunenthal samples.

21 MR. GLANDORF: Rob, let's go to the unclean slides
22 here. That is 541.

23 Q. And, Dr. Matzger, you just said -- I'd asked you if
24 you remembered testifying about the destruction of samples.
25 I believe your answer was you never testified that you were

1 unable to get the samples?

2 A. Correct.

3 Q. But look what you've written here in the slide.

4 You've actually wrote "Destruction of Samples," right?

5 A. Correct.

6 Q. That was your wording? You wrote that?

7 A. Yes.

8 Q. Now, do you have any information that these samples
9 were actually destroyed?

10 A. As opposed to what?

11 Q. This is your word, Dr. Matzger, destruction,
12 destroyed, as opposed to --

13 A. Retained.

14 Q. As opposed to retained?

15 A. As opposed to retained.

16 Q. Are those the two options in your mind, either
17 destroyed or retained?

18 A. Well, I don't -- I don't see -- I mean, you can
19 transform the sample onto something else, you know, make a
20 dosage of it, but I don't think that's relevant for samples
21 like CEP1a. The sample isn't consumed during the testing
22 like powder x ray diffraction testing, so if you decide to
23 discard the sample after analysis, I'd call that
24 destruction.

25 Q. Well, but what we're leaving out, here, though, is

1 that it is possible that it was used up through a variety of
2 different analytical techniques? That's one option;
3 correct?

4 A. Some of the -- some of the techniques would be more
5 difficult to recover the material from than others.

6 Q. You don't have any actual knowledge of the
7 circumstances by which these samples were used up or
8 destroyed, to use your word; correct?

9 A. No, I only have sort of the vague -- so they discuss
10 that some of the samples were -- disposed of or I don't know
11 what the term they used when there was a change in German
12 law. I would -- I would classify that as destruction of
13 samples. Then they had other possible explanations for
14 where it would be. It didn't seem like they had any
15 documentation of where the samples had gone.

16 Q. And if some of the samples were disposed of, according
17 to the change in German law, would that in your mind be an
18 unethical act?

19 A. So -- I don't know -- I understand there is some --
20 there is under the law and when you're prosecuting a patent,
21 there's some responsibility on the party to maintain samples
22 for questions that may reasonably arise during prosecution,
23 and there's some expectation of holding onto samples when
24 litigation is expected. I don't know all the nuances of
25 that, so that's not really a question for me to determine.

1 Q. Are you suggesting under patent law there was a
2 responsibility to retain these samples?

3 A. No, I was telling you I don't know.

4 Q. You don't know.

5 A. Yes.

6 Q. You don't know, but yet you were comfortable in
7 putting destruction of samples under the heading "unclean
8 hands"; correct?

9 A. Yes.

10 Q. Let's talk about your second area here, if we could.
11 Let's go back to patent -- this is Defendants' Exhibit 304.
12 Do you have that? When I say the patent, the '364 patent.

13 A. Yes. Okay.

14 MR. GLANDORF: Let's look at example 10, Rob.

15 A. Okay.

16 Q. You've got Example 10 in front of you, Dr. Matzger?

17 A. Yes, I do.

18 Q. Do you recall testifying about this example?

19 A. Yes.

20 Q. And could you please read for me the second-to-last
21 sentence here in this example?

22 A. "The x ray pattern for Form A is shown in Fig. 1, the
23 x ray pattern for Form B in Fig 4."

24 Q. Okay. Let's go now to Figure 4.

25 A. Okay.

1 Q. Figure 4 is on the fifth page of the exhibit.

2 Does Figure 4 show an XRPD pattern of Form B?

3 A. That's how it's labeled, that's how I interpreted it.

4 Q. Have you looked at the peaks to see if it is, in fact,
5 an XRPD pattern of Form B?

6 A. So I believe I have matched it up with the table, the
7 claims in the table, and I think it is consistent with that,
8 but as I said, there's some complexities because of the fact
9 that impurities are incorporated into the crystal lattice.

10 Q. As explained in Example 10, Figure 4 is, in fact, an
11 XRPD pattern of Form B. You aren't contesting the fact that
12 this is an XRPD pattern of Form B; is that right,
13 Dr. Matzger?

14 A. Well, no, I mean, this is what they're representing as
15 a pattern of Form B. Whether it -- and it certainly has the
16 characteristic peaks that we associate with Form B. How
17 pure the material is, it's -- it's not clear.

18 Q. Okay. Let's go now to -- let's fill in '364, let's go
19 to Example 2.

20 A. Okay. I'm there.

21 Q. Do you recall testifying about Example 2 today?

22 A. I do.

23 Q. Let's walk through this a little bit.

24 You testified about Example 2 as part of your
25 unclean hands argument. Do you recall that?

1 A. Yes.

2 Q. And I believe after you presented your unclean hands
3 argument with respect to Example 2, Ms. Sharkey asked you if
4 your opinion was limited to Example 2, and I recall you
5 saying that it was not. Does that sound right to you?

6 A. That's correct.

7 Q. What other examples here would your testimony about
8 unclean hands also apply to?

9 A. So they're all enumerated in my expert report.

10 I can point out one thing here that I forgot to
11 point out in my direct. So you see they claim here that the
12 material was examined by Raman microscopic analysis. I
13 believe that is not a true representation. The SSCI didn't
14 conduct Raman microscopic analysis on these samples.

15 Similar language is throughout. You can see it in
16 Example 3, they say the same thing, this is also not
17 examined by Raman microscopic analysis; 4.

18 So I've listed all of those in my expert report,
19 but in the interest of time, I didn't go through each one.
20 They're mostly the same story. The source of the material
21 was not accurately represented, and then aspects of the
22 characterization are not accurately represented.

23 Q. I'm sorry, we're looking to -- again, this is in my
24 mind a serious accusation when we talk about unclean hands
25 here, and I would like to know which examples you are

1 accusing.

2 You can't recall at this time?

3 A. So I -- as I recall -- well, so Examples 2, 3, 4, 5,
4 so they all have that -- the statement about Raman
5 microscopic analysis.

6 Q. Well, again -- and thank you for providing that
7 testimony on Raman microscopic analysis. You didn't show
8 any documents today relating to that theory, right? You
9 didn't show your basis for this opinion that they didn't
10 actually perform a Raman analysis of these examples?

11 A. Well, I can't show it. It's not there.

12 Q. You didn't show, I guess, a list of what SSCI did do.

13 A. So I think you can find it in the SSCI reports. Yes,
14 I mean, that was the basis. I looked through the SSCI
15 report and looked at what characterization they conducted.

16 Q. Okay. If your counsel is able to find that, we'll let
17 them find that, and I'd ask you about it.

18 But let's go back to what you did testify during
19 your direct testimony was, about whether these examples were
20 compared according to Example 25. Do you recall that?

21 A. Yes.

22 Q. And which examples does that criticism apply to?

23 A. I can't recall. I'd have to look back. It's pretty
24 well enumerated in my expert report, and I don't think
25 anything has changed since then.

1 Q. Okay. Well, let's just talk about Example 2, then, if
2 we could.

3 Now, Example 2, it starts off by saying -- the
4 first thing that's mentioned here in Example 2 is the
5 chemical name of tapentadol hydrochloride. Is that right?

6 A. Correct.

7 Q. And it refers then to Example 25 of the European
8 patent, which, as you testified, is for our purposes
9 equivalent to the '737 patent; is that right?

10 A. Correct.

11 Q. Now, according to the public at the time that this
12 patent, the '364, was filed, what methods were available to
13 the public to prepare tapentadol hydrochloride?

14 A. I'm not sure.

15 Q. One method that was available would be Example 25 of
16 the '737 patent or the European patent; is that fair?

17 A. Yes.

18 Q. Are you aware of any other methods that were available
19 to the public at the time of the filing of this patent to
20 prepare tapentadol hydrochloride?

21 A. It's not something I've investigated. I don't know.

22 Q. Now, the first step in Example 2 once you have your
23 tapentadol hydrochloride, the first step is then to dissolve
24 the tapentadol hydrochloride; is that right?

25 A. Yes.

1 Q. And when you dissolve the tapentadol hydrochloride, it
2 dissolves the crystal structure; isn't that correct?

3 A. That is correct.

4 MR. GLANDORF: Let's go back to the unclean hands
5 slide, Rob, which is 41.

6 Q. We're going to talk now about the first bullet point
7 here, that "Grunenthal knew by 2001 that Form A was
8 ubiquitous."

9 Do you recall that testimony, Doctor?

10 A. I do.

11 Q. Let me make sure I understand this here. Is your
12 testimony that Grunenthal should have known at that time
13 that Form A was ubiquitous, or are you testifying that they
14 did know that Form A was ubiquitous?

15 A. They did know.

16 Q. They did know. That's your testimony.

17 A. Yes.

18 Q. And because they did know, it was unreasonable for
19 them to seek this patent; is that your testimony?

20 A. No.

21 Q. You say they have unclean hands because they knew that
22 Form A was ubiquitous. How does that knowledge lead to a
23 ground for unclean hands?

24 A. Well, it's certainly not the only ground, but what you
25 see from those is a picture of Form A being everywhere, that

1 they find that internally, they find it when they send out
2 to companies that that's the easy form to make, Form B being
3 rather difficult to make. And then what they represent to
4 the Patent Office is quite the opposite, which is that the
5 only thing that could be made in the prior art was Form B,
6 and we've, you know, all of a sudden discovered Form A. So
7 that's the contrast being drawn.

8 Q. Let's go to slide -- thank you. Let's go to slide 43,
9 if we could, to look at some of these examples here.

10 You testified about this slide, do you recall?

11 A. Yes.

12 Q. This is about the SSCI investigation; correct?

13 A. Correct.

14 Q. And what year was this? What time period is this
15 from?

16 A. 2001.

17 Q. And Ms. Sharkey asked you that question, right, and
18 you said 2001; do you recall that?

19 A. Yes.

20 Q. Let's look at the next slide, 44. This slide is also
21 about the SSCI investigation; is that right?

22 A. Yes.

23 Q. And again, what's the time period for this slide?

24 A. It's again about 2001.

25 Q. About 2001. Okay.

1 Let's keep moving, and let's go to slide 44.

2 Sorry, 45.

3 What's the title on this slide?

4 A. "Results so far."

5 Q. "So far." These are the results so far.

6 Do you know what time period this slide is from?

7 A. I believe this is 2001.

8 Q. I believe it is, 2001.

9 MR. GLANDORF: Let's pull up, if we could, -- I'm
10 going to pull up a demonstrative from an earlier witness
11 that I think the Defendants have.

12 Let's go back -- can we go back to the Gruss
13 demonstratives and pull up the final timeline?

14 Q. You may not have seen this slide. Have you seen this
15 slide previously, Dr. Matzger?

16 A. No, I have not.

17 Q. Okay. And I'm not going to assume that you agree that
18 it's correct or anything like that. I just want you to kind
19 of reference ourselves.

20 There's an entry up here for April 2001. Do you
21 see that?

22 A. I do.

23 Q. It says "Grunenthal commissions SSCI to perform a
24 polymorph investigation on tapentadol hydrochloride." Do
25 you see that?

1 A. I do.

2 Q. And you just testified that the SSCI documents that we
3 were looking at in your slides, slides 43, 44, 45, those all
4 related to an SSCI investigation in 2001; is that right?

5 A. All of them? So I think two of them related to the
6 SSCI investigation.

7 Q. I see. You're right, and the third one we didn't
8 necessarily establish as SSCI, but you testified it was from
9 2001 as well.

10 A. Yes, I think it's Grunenthal because they're talking
11 about the synthesis. I think it's internal Grunenthal data
12 because they're talking about the synthesis, which I don't
13 understand SSCI to have done.

14 Q. And the patent is filed later; the patent is filed in
15 June 2004.

16 A. Correct.

17 Q. Well, let's go back to your last slide there, which
18 was slide 46.

19 I believe Ms. Sharkey asked you here to identify
20 which bullet points were relevant to your opinion, or a
21 similar question. Do you recall that?

22 A. I do.

23 Q. And you read, in fact, from the last bullet point, did
24 you not?

25 A. That's one of the things I read, yes.

1 Q. Let's look at that again. Could you read that bullet
2 point, the last one, one more time?

3 A. "The only challenge in the polymorphism of CG5503 was
4 the shifting in the DSC thermal events and the few cases
5 where Form B appeared and seemed to be stable at room
6 temperature."

7 Q. And what is meant by DSC thermal events?

8 A. So there's -- there was actually quite a lot of DSC
9 data that I didn't talk about. It was internal, it's not
10 included in the patent, where they've been able to show the
11 conversion of Form A to B and B to A in some cases.

12 Q. And what does it mean -- when it says there's -- well,
13 when it says there's shifting in the DSC thermal events, do
14 you understand that to mean that the temperature at which
15 these conversions happen seems to shift up and down in
16 temperature?

17 A. That's my understanding.

18 Q. And then there's a clause at the end here where it
19 says there are a few cases where Form B appeared and seemed
20 to be stable at room temperature.

21 A. Yes.

22 Q. Is that correct?

23 This is Grunenthal's knowledge; this is a
24 Grunenthal document; is that right?

25 A. Yes.

1 Q. And Grunenthal at this point in time, 2005, had an
2 understanding that there were cases where Form B appeared
3 and was stable at room temperature; is that right?

4 A. That's their understanding of what was going on, yes.

5 Q. And just to be clear, when I asked you earlier, we
6 weren't talking about what Grunenthal should have known.
7 You were testifying as to what Grunenthal knew, and your
8 testimony is that Grunenthal knows that Form A is
9 ubiquitous.

10 Here, we have Grunenthal stating that there are
11 cases of Form B that are stable at room temperature. Is
12 that right?

13 A. Yes, I don't know if that's exclusively Form B, but
14 yes, they're saying they saw cases of Form B that were
15 stable at room temperature.

16 Q. Let's go then to a new exhibit. Let's go to DTX 1009,
17 one zero zero nine.

18 A. Do I have it?

19 Q. You should have it in our cross binder.

20 A. Okay.

21 Okay.

22 Q. Have you seen Defendants' Exhibit 1009 previously,
23 Doctor?

24 A. Yes.

25 Q. Did you consider it when coming to your opinions that

1 you presented today?

2 A. Yes, I think I used Table 4 out of it in one of my
3 slides.

4 Q. Let's look here on the first page of this exhibit.

5 It mentions that polymorph B is metastable at room
6 temperature. Do you see that?

7 A. Yes.

8 Q. And then let's go on to the second page, if we could.

9 A. Okay.

10 Q. It says here "Batches -- " -- let me make sure I find
11 where we are. We are underneath the heading "Investigations
12 on the Polymorphic Properties of the Drug Substance." Do
13 you have that section?

14 A. I do.

15 Q. I'll have you read it. Will you read that first
16 sentence that starts "Batches"?

17 A. "Batches from the Process Development Department
18 usually consist of polymorphic Form A. Figure 2 shows the
19 DSC results of one of these ordinary batches."

20 Q. Okay. And just for reference here, we're on
21 GRTNUVO0002195. Correct?

22 A. Correct.

23 Q. And what it says is that batches from Process
24 Development usually consist of Form A; correct?

25 A. Correct.

1 MR. GLANDORF: Let's go on then to the third page,
2 and, Rob, let's go ahead and -- that second paragraph
3 starting with other processed batches, let's zoom in on
4 that.

5 Q. Dr. Matzger, do you see that paragraph we're referring
6 to there on the third page of this exhibit?

7 A. Yes.

8 Q. And go ahead and read the first -- those two sentences
9 there.

10 A. "Other processed batches indicate a more complicated
11 picture of the transition. In some batches the transition
12 temperature is significantly decreased, so that at room
13 temperature Form B seems to be metastable."

14 MR. GLANDORF: Okay. And now let's go all the way
15 back to the front of this document, and, Rob, if you want to
16 highlight that first paragraph under "General."

17 Q. Dr. Matzger -- and this report is referring to work
18 that was conducted by SSCI for Grunenthal; is that right?

19 A. I don't know if that's the only basis of the report.
20 It's clearly one of the bases.

21 Q. And this report is indicating that Grunenthal had an
22 understanding that you would sometimes have Form B at room
23 temperature; isn't that true?

24 A. They said they sometimes had batches where Form B
25 seems to be metastable. Doesn't say anything about pure

1 Form B, though, in the absence of Form A.

2 Q. Let's go now to -- right. I'm sorry. It just refers
3 to batches of -- just refers to Form B; is that right?

4 A. It just discusses the Form B, yes.

5 Q. Let's look at another document here.

6 THE COURT: Just on 1009, do we have a date on
7 that document?

8 MR. GLANDORF: I don't know if we do. Let me
9 confer.

10 THE COURT: Okay.

11 (Off the record discussion among counsel)

12 THE WITNESS: If you want me to keep reading on
13 that document, there's a lot of interesting stuff just on
14 the next few lines.

15 THE COURT: You'll have to wait for a question.

16 THE WITNESS: I'm sorry.

17 THE COURT: That's okay.

18 MR. GLANDORF: I don't know that we have a date
19 right now. We'll look for it and we'll find one and get
20 back to you.

21 THE COURT: Thank you.

22 Q. Let's go on to Plaintiff's Exhibit 509, if we could.

23 And we have a translation as well.

24 A. Thank you.

25 Q. This is the translation, which is 509T, so they should

1 follow one after the other in the document.

2 Will you read the first two sentences of the body
3 of the text here?

4 A. "The 2 filled samples have been sent. Now I still
5 have two new samples here. However, CG5503 CEP1a and
6 CEP2a, which appear to still be Form B (after eight months,
7 double exclamation marks)."

8 Q. Double exclamation point. Two exclamation points, is
9 that what you're saying?

10 A. Yes, because it's so surprising that they're finding
11 Form B in this ubiquitous Form A world that they've been
12 experiencing.

13 Q. That's right, it was a surprise to them. What's the
14 date, August 2001?

15 A. Yes.

16 Q. You see that?

17 A. Yes.

18 Q. They were surprised in light of their earlier
19 knowledge to find these stable Form B's. Is that your
20 testimony?

21 A. These stable things that they interpret as Form B.

22 Q. Okay. That's their interpretation. You may disagree,
23 but according to this document, that's their -- that's
24 Grunenthal's interpretation. Is that fair?

25 A. It's one person at Grunenthal. I don't -- I don't

1 know whether that's all of -- whether that's Grunenthal's
2 understanding. It's an e-mail of one person to another, and
3 I don't see the response.

4 Q. I see. And let's look at who this e-mail is between.

5 It's from Dr. Andreas Fischer. Do you recognize
6 that name in the context of our --

7 A. I do.

8 Q. And who is he?

9 A. He's one of the inventors.

10 Q. And who is he writing to here?

11 A. Dr. Gruss.

12 Q. And Dr. Gruss is?

13 A. I believe so, I think he's the one who was doing the
14 powder x ray diffraction on some of the samples at this
15 point.

16 Q. He's also an inventor on this patent, isn't he?

17 A. I believe so.

18 Q. Did you hear his testimony --

19 A. No.

20 Q. -- last week?

21 Okay. Let's move on, then, to a new exhibit here,
22 Plaintiff's Exhibit 555.

23 A. Okay.

24 Q. Now, I understand you testified that you don't speak
25 German. Is that correct?

1 A. That is correct.

2 Q. Do you see the name of, you know, Grunenthal's
3 batch-naming convention here over on the left where it says
4 BN 200 hash sign 0? Do you see that?

5 A. I do.

6 Q. And are you familiar with a batch labeled as hash
7 zero?

8 A. Yes.

9 Q. And as far as you know, this has been discussed in
10 this litigation as batch zero or batch number zero?

11 A. That's my understanding.

12 Q. And the indication here is that it's Form B; is that
13 correct?

14 A. So, yes, I don't -- I can't read the other -- is there
15 a translation, perhaps, of what's going on on the right?

16 Q. I don't know that we do have a translation of this
17 one.

18 Is your recollection, though, that batch zero --
19 batch number zero tested to be Form B?

20 A. That's my understanding.

21 Q. Okay. Let's go on, then --

22 MS. SHARKEY: Your Honor, I think the translation
23 is in the next tab if he wants to look at that.

24 MR. GLANDORF: Thank you very much.

25 THE COURT: Okay.

1 Q. Dr. Matzger, the translation is in the next tab.

2 A. Either it's a bad translation or I don't understand
3 it. I don't know what free of phases means.

4 Q. I'm okay with that. Your testimony is that you recall
5 batch zero having tested as Form B; is that right?

6 A. Yes, that's my understanding, but the interpretation
7 of the powder x ray diffraction pattern was that it was Form
8 B.

9 Q. Okay. Let's go now to DTX 1242, which I believe is in
10 your binder, we were looking at it moments ago, it's on one
11 of your slides, but I believe it's in your binder, in the
12 direct examination binder.

13 A. 1242. Okay.

14 Q. Do you have it?

15 A. I do.

16 Q. And if we go to slide -- I believe it's slide 13, it's
17 Bates number 129619.

18 We looked at this table a moment ago. Do you
19 recall that?

20 A. I do.

21 Q. It's one of the tables you relied on?

22 A. Yes.

23 MR. GLANDORF: Okay. Let's go now to page 18,
24 Rob.

25 Q. Have you seen this page before as well, Dr. Matzger?

1 A. I mean, I've certainly seen these sentiments if not
2 this exact page.

3 Q. These sentiments. All right. Let's look at the
4 second sentence, please, if we could, "In special cases..."
5 Do you see that?

6 A. Yes.

7 Q. Would you read that for the Court?

8 A. "In special cases Polymorph B was obtained and seemed
9 to be stable at room temperature."

10 Q. Seemed to. Were you emphasizing the word "seem"
11 there?

12 A. Yes.

13 Q. Here's Grunenthal's understanding, though, that it
14 seemed to them, right, that there were cases where polymorph
15 B was obtained and stable at room temperature. Is that
16 fair?

17 A. So, again, we don't know anything about the purity
18 here, but they say yes, it seems to be stable at room
19 temperature, and this is Grunenthal's understanding.

20 Q. I want to go back to the beginning, then, when I asked
21 you. Again, this is a -- this is all underneath your
22 heading of unclean hands; correct? You analyzed this
23 document as part of your --

24 A. Oh, as part of the analysis, yes.

25 Q. Where you were arguing that Grunenthal was making

1 misrepresentations to the Patent Office; is that fair? This
2 is part of your argument that Grunenthal was making
3 misrepresentations; isn't that true?

4 A. Yes.

5 Q. That they were engaging in fraud with the Patent
6 Office? Would you say that?

7 A. Again, that's probably a legal opinion. I don't want
8 to venture into that area.

9 Q. Okay. But in this particular batch, this particular
10 bullet point, your argument was that Grunenthal knew that
11 Form A was ubiquitous. Isn't that what you said?

12 A. Yes.

13 Q. Now, we've looked at a variety of documents here where
14 they are talking about stable Form B that they're finding.
15 You may have been surprised, there may have been two
16 exclamation points, but they are discussing Form B in a
17 variety of circumstances. Isn't that fair?

18 A. Yes.

19 Q. What's your knowledge of ubiquitous? I mean, what's
20 your definition of ubiquitous here, then?

21 A. That they're getting it everywhere, they're getting it
22 under all kinds of conditions, that it's not a particularly
23 special observation that Form A appears. It's everywhere.

24 Q. So it's your testimony that they knew Form A was
25 ubiquitous except for cases when it wasn't?

1 A. I'm sorry, I did not mean to say by ubiquitous that
2 there's only one form. It's known there are two forms.
3 There's Form A and Form B. What I was emphasizing when I
4 said it was ubiquitous is that it is obtained by them, it's
5 obtained by Crystallics, it's obtained by SSCI. It's
6 continually uncovered, that form, rather than Form B.

7 Q. So your testimony is not that -- and let's step back
8 here.

9 There's no debate that there are two forms that
10 exist; correct?

11 A. No. No.

12 Q. The debate is whether or not Form B exists and can be
13 stable at room temperature; is that -- that's the debate
14 here, correct?

15 A. I think the debate is whether that prior art form was
16 produced by Example 25 of the '737 patent.

17 Q. Well, that's not what you're testifying about here,
18 though. You're testifying that polymorph A was ubiquitous,
19 that it was everywhere; isn't that correct?

20 A. Yes, but I -- I didn't -- didn't mean to imply that
21 that's the only form. Certainly Form B is a real form.

22 Q. It's a real form at room temperature; correct?

23 A. Well, that, I don't believe. I don't think there's
24 any evidence that there's a pure tapentadol hydrochloride
25 Form B that's stable at room temperature.

1 Q. Your belief is that there's no Form B stable at room
2 temperature. Grunenthal's belief is that there are cases
3 where Form B was stable at room temperature. Isn't that
4 fair?

5 A. Well, no, you can look right down on the slide here.
6 They're saying that this has a mixed crystal formation as a
7 potential -- they realize there's something off with this
8 result, because they understand as a matter of science when
9 you have a phase transition and an established relationship
10 in thermodynamics between two forms that there's a stability
11 relationship that occurs at a particular temperature. They
12 recognize that, and now they're trying to explain this
13 anomalous result that they have of this stability under
14 conditions where the material shouldn't be stable, and
15 they're offering several reasons why that may be occurring
16 right here.

17 Q. That's right. They are saying that there is in some
18 cases Form B that's stable at room temperature. They're
19 offering reasons for that. The question is, what I'm
20 missing here, Doctor, is why these reasons mean that the
21 ubiquity, as you say, of Form A leads to a conclusion that
22 there was some kind of unclean hands conduct before the
23 Patent Office. Can you explain that?

24 A. So certainly that alone is not -- I don't think would
25 be a basis for unclean hands necessarily. It depends on

1 what is, you know, what is shared with the Patent Office, I
2 think.

3 Q. And one of your challenges here is that polymorph B
4 doesn't result from the prior art. Isn't that one of the
5 arguments that you're making?

6 A. Yes, that certainly there's no basis for that
7 statement.

8 Q. And here these possible reasons here, impurity
9 profile, particle size, mixed crystal formation, none of
10 those characteristics are proscribed or limited in any way
11 by the prior art; right? None of those characteristics are
12 limited by Example 25 in the '737 patent; isn't that true?

13 A. No, there is some information about the purity of the
14 material from the -- from Example 25. Now, you asked me if
15 there was a purity spec. There is not a purity spec. But
16 there is information about the color and about the melting
17 point. This is the data that I have, so this is what I can
18 analyze.

19 Q. To be fair, we looked at Example 25. There was no
20 information about the color there; correct?

21 A. So that comes -- well, you might have also noticed in
22 Example 25 the melting point was wrong, too. So there are a
23 couple of issues there, right? But this is stuff that was
24 later disclosed and that were properties of the product of
25 Example 25.

1 Q. And again, you have a line in your head in terms of
2 how close they have to be to those characteristics in that
3 Example 25, you have a line in your mind for when it's a
4 faithful reproduction and when it's not; correct?

5 A. Well, I don't know exactly what that line is. I can
6 tell as you move away from that line, it can be -- it can be
7 very clear, but sure, there will be a gray area somewhere.
8 But I don't think we're -- we're near that gray area in
9 these cases.

10 MR. GLANDORF: If I could confer one time quickly,
11 Judge?

12 THE COURT: Yes. Yes.

13 (Off the record discussion between counsel)

14 BY MR. GLANDORF:

15 Q. I do have just one more thing to check with you,
16 Dr. Matzger, and this relates to your testimony about the
17 Raman spectroscopy. Do you recall that?

18 A. I do.

19 MR. GLANDORF: Rob, do you have Dr. Matzger's
20 opening report? Can you go to paragraph 60?

21 Q. Do you recall testifying in your report about whether
22 SSCI used Raman spectroscopy?

23 A. I believe I did.

24 Q. Okay.

25 A. I don't know whether it was in the opening report or

1 in the rebuttal report.

2 Q. And here, you wrote that "SSCI used x ray powder
3 diffraction, differential scanning calorimetry,
4 thermogravimetry, hot stage microscopy, moisture balance,
5 infrared and Raman spectroscopy to characterize crystal
6 forms produced during the screen." Do you see that?

7 A. I do.

8 Q. Does that refresh your memory that SSCI did use Raman
9 spectroscopy?

10 A. You're confusing Raman spectroscopy with what's stated
11 in the patent.

12 Q. And what's stated in the patent?

13 A. Raman microspectroscopy or microscopy.

14 Q. And that's certainly what you've written here; is that
15 right?

16 A. Yes, one of the techniques, the Raman microscopy, is
17 very well suited to finding impurities in samples at low
18 levels, and the bulk form of Raman spectroscopy is much less
19 suited to do so.

20 MR. GLANDORF: No further questions.

21 THE COURT: Thank you. Thanks very much.

22 Anyone?

23 MS. SHARKEY: We have no further questions.

24 THE COURT: All right. That concludes the
25 testimony of this witness.

1 Thank you very much for coming in and assisting us
2 today, and you may be released from the stand.

3 Thank you.

4 (Witness excused)

5 MS. SHARKEY: Your Honor, do you mind if I get
6 that binder back?

7 THE COURT: Go ahead.

8 MS. SHARKEY: Thank you.

9 MR. FITZPATRICK: Your Honor, we have binders to
10 hand out.

11 THE COURT: Yes, please do, and then let's get the
12 comments and then we can continue.

13 MR. CAPUANO: Your Honor, I'm sorry.

14 THE COURT: Yes, go ahead.

15 MR. CAPUANO: We submitted prior art binders on
16 the 7th, I think, including those of the '593 patent, and I
17 think that's probably the more focused set of exhibits for
18 this witness.

19 THE COURT: That sounds fine.

20 MR. FITZPATRICK: May I approach, Your Honor?

21 THE COURT: Yes.

22 MR. CAPUANO: Your Honor, we also have some
23 chemical models.

24 THE COURT: That sounds good. Where are they?

25 Oh, they're right in front of you. I'm sorry.

1 MR. CAPUANO: These are two different things.

2 THE COURT CLERK: These are for her?

3 MR. CAPUANO: Yes. You'll have to share.

4 (Laughter)

5 THE COURT: Thank you. Put them right up here.

6 MR. CAPUANO: Don't take them apart because we'll
7 never get them --

8 THE COURT: I'm not. Actually, how tightly bound
9 are they?

10 MR. CAPUANO: They're tightly enough. You can
11 handle them.

12 THE COURT: Thank you.

13 (Models were handed up to the Court.)

14 MR. CAPUANO: They're not identical. We'll
15 explain.

16 THE COURT: Yes, I know. Thank you.

17 MR. CAPUANO: And if I could add, Your Honor,
18 these are -- well, first of all, Defendants would like to
19 call Professor Stephen Martin to the stand, Your Honor.

20 THE COURT: All right. Shall we bring him up and
21 then we can talk about all the related materials?

22 MR. CAPUANO: Yes.

23 THE COURT: Let's have the witness come up.

24 Let us have the witness sworn in.

25 Good afternoon. How are you?

1 THE WITNESS: Good afternoon. How are you?

2 THE COURT: Good, thank you.

3 THE COURT CLERK: Raise your right hand, left hand
4 on the bible.

5 S T E P H E N F. M A R T I N, called as a witness on
6 behalf of the Defendants, and having been duly sworn,
7 testified as follows:

8 THE COURT CLERK: Please step up and state your
9 name for the record.

10 THE WITNESS: My name is Stephen Martin,
11 S-t-e-p-h-e-n, M-a-r-t-i-n.

12 THE COURT: Thank you very much.

13 All right. Let's go down the list of items that
14 we have to discuss before we get to the witness.

15 Have you looked at the exhibits on both sides?
16 Have we taken a look? Any issue?

17 MR. BEST: We've done so, Your Honor, and we see
18 no issues.

19 THE COURT: All right, and the demonstratives as
20 well?

21 MR. BEST: Correct.

22 THE COURT: No issues. Very well. Okay.

23 MR. CAPUANO: Thank you, Your Honor.

24 Vince Capuano for Actavis.

25 THE COURT: Thank you.

1 MR. CAPUANO: We've handed out, in addition to the
2 demonstrative exhibits we're going to show on the screen and
3 that we've passed out, some chemical models. These are
4 Professor Martin's chemical models.

5 As I understand it, they don't make these anymore.
6 You can sometimes get them off of E-bay or craigslist.

7 THE COURT: Because I was going to say, we have
8 the plastic versions put together. These look very nicely
9 done.

10 (Laughter)

11 MR. CAPUANO: And what we'd ask is that Plaintiffs
12 return them at the end of the testimony, or even at the end
13 of the trial if they think they need them, you know, but
14 that -- the Court can keep them, and then maybe after the
15 case has been closed, we could have somebody come and pick
16 them up.

17 THE COURT: That sounds perfectly fine. Thank
18 you.

19 How much do I have to worry about breaking these?
20 Are these soldered?

21 (Laughter)

22 THE WITNESS: Oh, no, you won't break them.

23 THE COURT: All right.

24 MR. CAPUANO: They're not soldered, though. They
25 can be pulled apart.

1 THE COURT: They're not. So we'll be gentle with
2 them.

3 THE WITNESS: I'll give a tutorial on how to play
4 with them.

5 THE COURT: Very well.

6 MR. CAPUANO: There may come a time when Professor
7 Martin may want to add something to the model, so he's got a
8 little box of stuff.

9 THE COURT: I understand.

10 MR. CAPUANO: May I proceed, Your Honor?

11 THE COURT: Yes, go right ahead.

12 DIRECT EXAMINATION

13 BY MR. CAPUANO:

14 Q. Do you have a binder of exhibits up there?

15 A. I have three binders, yes.

16 Q. Okay. Does one of them say "Stephen Martin"?

17 A. One of them says "Defendants' Key Prior Art
18 References," one of them says "Stephen F. Martin Ph.D.
19 Exhibits," and one of them says "Depomed and Grunenthal."

20 This one here?

21 Q. Okay. Thank you.

22 THE COURT: And again, the one that says
23 "Defendants' Key Prior Art References," those were the five
24 copies that you had previously submitted. We just brought
25 them out and handed them out, which is what you requested,

1 correct?

2 MR. CAPUANO: Correct, and each of those is also
3 in the exhibit book.

4 THE COURT: Okay.

5 BY MR. CAPUANO:

6 Q. Good afternoon, Professor Martin.

7 A. Good afternoon.

8 Q. Just for the record, would you please state your full
9 name?

10 A. My name is Stephen Frederick Martin.

11 Q. Okay. And where are you currently employed, Professor
12 Martin?

13 A. I'm employed at the University of Texas at Austin.

14 Q. Okay. And what is your position there?

15 A. I'm a professor of chemistry, and I hold the M. June
16 and J. Virgil Wagner Chair in chemistry.

17 Q. And to help the Court understand and for you to
18 explain your opinions in this case, have you prepared a set
19 of demonstrative exhibits?

20 A. I have.

21 Q. Okay. Let's start with the first one.

22 Professor Martin, could you tell us about your
23 experiences and expertise, including your experiences and
24 expertise related to analgesics?

25 A. Sure.

1 Generally speaking, my experience is in synthetic
2 organic, bio-organic, and medicinal chemistry. I've got
3 extensive experience in the design, synthesis, and
4 optimization of small molecules that bind to biological
5 targets, especially proteins.

6 We've been involved in methods and synthesis of
7 compounds that are biologically active, and in that context,
8 we've studied activity of structure, activity relationships,
9 and we've worked on compounds that have activities ranging
10 from anti-cancer, African sleeping sickness, and then a
11 variety of neurological disorders, including
12 neurogeneration, addiction, pain, and the like.

13 Q. Okay. Professor Martin, you said structure activity
14 relationships. Can you explain what is a structure activity
15 relationship or the study related to structure activity
16 relationships?

17 A. Sure.

18 Generally speaking, what it involves is, we take
19 -- we start with a particular compound and we want to study
20 the effects of making structural changes on that molecule on
21 some property, and so if it's for some activity, say
22 analgesia, we would make a structural change in the
23 molecule, we would examine what the impact of that change
24 was on its analgesic effect, we'd make a number of
25 structural changes, some of these changes would be good,

1 some of them would be bad, but in that process, you get a
2 sense for things that you can do to improve the situation,
3 let's say improve the analgesic properties or lead to
4 deterioration or loss of those properties.

5 Q. Okay. And when you say "we," do you have a research
6 group in Texas?

7 A. I do.

8 Q. Okay, and can you describe the composition of your
9 research group today and maybe over the years?

10 A. Yes. It's typically been a number of graduate
11 students ranging in number from, oh, 12 to 15 or 16 in the
12 last 10 or 15 years. Now I've got about 12 graduate
13 students. I've had a lot of postdocs over the years. I've
14 mentored a number of undergraduates over the years, so
15 currently I have five undergraduates working in my lab. I
16 have one research associate working in my lab. I don't have
17 any postdocs at the moment.

18 Q. And are the people who work in your lab, the postdocs
19 and graduate students and undergraduates, are they involved
20 in the synthesis of organic chemicals?

21 A. Yes, they are.

22 Q. Okay. And do you also do, for example, when your
23 group is involved in a structure activity relationship
24 study, does your group do the testing of the activity?

25 A. It depends. It depends on what the activity is.

1 Right now, we're doing both. Some compounds we send out for
2 testing, and some compounds we test ourselves.

3 Q. Okay. And have you had occasion or experience in your
4 research group over the years to work on compounds that are
5 analgesics?

6 A. Yes, I have. In fact, one of the first things I did
7 as a professor at the University of Texas, I had a small
8 contract with a small company for making methadone
9 derivatives, so I had that experience.

10 Early also in my career, we made a number of
11 compounds that are structurally closely related to morphine.
12 Morphine, in fact, was one of those molecules that I had on
13 an NIH proposal as a compound that I wanted to make. We
14 never made it, but it was a compound we were interested in
15 the synthesis of.

16 We also had looked at the enkephalins. The
17 enkephalins are peptides. They're the body's natural
18 opioids. They're the compounds, they're the peptides in
19 your body that interact with the so-called opioid receptors
20 and suppress the feeling, the sensation of pain of
21 analgesics, like morphine, and we had a program where we
22 were modifying the structures of these enkephalins, trying
23 to get analogues that would bind better.

24 Q. And when you say "bind better," do you mean bind
25 better to -- to what?

1 A. Bind better to the opioid receptors. We were looking
2 for compounds that would bind better to each one of them. I
3 mean, we were interested in the selectivity of binding
4 because that turns out to be important in the area.

5 We were also interested in the functional activity
6 of these compounds because there are two kinds of functional
7 activities: There are those compounds that are agonists,
8 that is, they elicit the biological response, for example,
9 in this case, of morphine, or they're antagonists, which in
10 this case would be to suppress the effects of morphine, the
11 agonist.

12 Q. And I think you mentioned methadone derivatives. What
13 is methadone?

14 A. Methadone is actually a very highly simplified
15 analogue of morphine. It's an opioid. It's been used for
16 years both as an analgesic and also for -- I think to try to
17 get people off of opioids.

18 Q. In your experiences and your career, Professor Martin,
19 have you had occasion to consult with any pharmaceutical
20 companies?

21 A. I have. I've consulted with a number of major
22 companies - Abbott, Pfizer, Merck.

23 Q. And in your career, have you served as an editor for
24 any journals?

25 A. Yes, I've been an editor of Tetrahedron for the

1 Americas since about 1992. This is an international journal
2 with a focus in generally organic chemistry, all areas of
3 organic chemistry. As a member of -- as an editor of that
4 journal, I'm also on the editorial advisory board of a
5 family of journals, a suite of journals. There are five
6 journals in that particular family. Some are medicinal
7 chemistry journals, bio-organic chemistry journals, and
8 others are journals involved with focus on stereochemistry.

9 I've also been an editor of a series called
10 "Organic Syntheses." This particular series is a book, a
11 series of books, collection of books wherein various people
12 who are editors, and this checks submitted procedures for
13 preparing compounds, check the procedures for
14 reproducibility and so forth.

15 Q. And in your experiences throughout your career,
16 Professor Martin, did you become familiar with what's
17 sometimes called a lead compound?

18 A. Yes, I have.

19 Q. Okay. And what is a lead compound in the field of
20 medicinal chemistry?

21 A. Well, generally speaking, it's a compound that serves
22 as a lead for further investigation. So I mentioned
23 structure activity relationships a minute ago. You would
24 start with a lead somehow, and that would be the compound
25 that you would modify.

1 There are different ways of getting leads. I
2 could talk about that if you want.

3 Q. Please do. What are the different ways of identifying
4 a lead or lead compounds?

5 A. The different ways, we look to nature sometimes for
6 compounds in nature that have beneficial biological
7 activity, and then those compounds are our lead compounds
8 and the ones we might modify.

9 Sometimes a compound is a drug, and you might want
10 to develop analogues of that drug, and so that drug becomes
11 a lead compound.

12 Lead compounds also are identified today in
13 screening processes. So a company will have a certain
14 biological target they're interested in, some enzyme or
15 something of that sort. They will develop an assay, and
16 they will then screen sometimes tremendously large numbers
17 of compounds to look for compounds with activity, and then
18 they will find some, and from that group that they find will
19 emerge one or more lead compounds, actually.

20 Q. Okay, and that anticipated my question. Is there
21 always in a project like this just one lead compound?

22 A. No.

23 Q. Okay, and why and in -- what would cause there to be
24 more than one lead compound?

25 A. Well, there might be several compounds that have maybe

1 different structures but similar properties, and so those
2 different compounds would all be independent leads, for
3 example.

4 Q. Okay. And when you consider starting with a lead and
5 making changes, structural changes to a lead compound, do
6 you make just one change, or do you sometimes make more than
7 one changes to a lead compound?

8 A. Well, I think generally you like to make one change at
9 a time at the beginning because you don't want -- you want
10 to minimize the structural changes that you make because you
11 want to do this incrementally to find out what the effect of
12 incremental changes are, and then as you learn, you make
13 bigger changes and bigger changes, and pretty soon you start
14 making multiple changes and, you know, it kind of depends.
15 It's an iterative process. The's sort of driven by the
16 biological results that you obtain as you make these
17 structural changes.

18 Q. Okay. And in your consulting with pharmaceutical
19 companies, is that approach that you just mentioned
20 consistent with the way drug discovery happens at
21 pharmaceutical companies?

22 A. Yes, it is.

23 Q. In your time at the University of Texas, have you had
24 responsibilities for teaching?

25 A. Yes, I have.

1 Q. Okay. Can you tell us about some of those?

2 A. Yes. I have taught courses really only in the general
3 area of organic chemistry; sophomore organic chemistry,
4 that's an undergraduate level introductory course; upper
5 division courses in organic chemistry; lecture courses to
6 undergraduates. I teach an advanced undergraduate lab
7 course. At the graduate level, I've taught a number of
8 courses in advanced synthesis and heterocyclic chemistry,
9 bio-organic chemistry, all generally under the broad
10 umbrella of organic and bio-organic chemistry.

11 Q. Okay. Professor Martin, can you take us through your
12 educational background, beginning with college?

13 A. Yes. I was an undergraduate at the University of
14 New Mexico, and I got my B.S. degree in 1968. I then went
15 to Princeton University -- well, I should say, I guess, that
16 I majored in organic chemistry, or in chemistry, I should
17 say, when I was in college. I had a math minor.

18 When I went to graduate school, my focus was in
19 organic chemistry with the subspecialty of heterocyclic
20 chemistry. I graduated from Princeton in '72. I got a
21 Master's along the way because it's what you did, it just
22 happened.

23 And then I went to the University of Munich as a
24 postdoc, where I was -- I was there for about 15 months in
25 Munich, and I worked again in the general area of

1 heterocyclic chemistry, straining compounds.

2 And then I went to Massachusetts Institute of
3 Technology, again working in the general area of
4 heterocyclic chemistry, in this case, alkaloids, alkaloid
5 synthesis. Alkaloids are a type of natural product that
6 contain nitrogen, like morphine.

7 Q. And throughout your career, have you published your
8 work in peer-reviewed journals?

9 A. I have. I have. I've got some 320 publications in
10 refereed journals. Thirteen published books - basically,
11 this is a series of editions and second editions, third
12 editions of an undergraduate laboratory textbook that I'm
13 the co-author of. I like to say it's popular. I wish it
14 were more popular, but yes.

15 And I'm an inventor on some patents that we've
16 done recently in the context of some of our work on
17 neurological disorders.

18 Q. And throughout your career, Professor Martin, have you
19 been selected for any honors or awards?

20 A. Yes, I have some. I've listed some. Some go back to
21 sort of the time -- I included some that go back to the
22 time, in the time frame, really, of the patent at issue. So
23 I was an NIH Career Development awardee; American Cyanamid.
24 So there are various companies that give out certain kinds
25 of awards, and I had some of those.

1 The Pettit Centennial Professor of Chemistry is an
2 internal recognition in the department. It's an endowed
3 position that was conferred based on my scientific
4 accomplishments.

5 I also received the Alexander Von Humboldt Prize
6 in 1995, and that carried with it an obligation to spend six
7 months in Germany, and I took that over two different
8 summers.

9 An ACS Award; the Arthur C. Cope Scholar Award.

10 Now, as I said earlier, I'm the M. June and
11 J. Virgil Wagner Chair in chemistry.

12 Received the Japan Science Award for the promotion
13 of science.

14 And maybe most recently, this International
15 Society of Heterocyclic Chemistry Senior Award.

16 Q. Very well.

17 Professor Martin, can you tell us, have you had
18 occasion to serve as an expert witness in any legal matters?

19 A. I have.

20 Q. And could you tell us about some of those, with
21 particular focus on those cases where you provided either
22 deposition or trial testimony?

23 A. Yes. So 13 cases where I basically was involved at
24 various levels. It sort of got up to the point of maybe a
25 deposition. Sometimes it was writing some expert things for

1 attorneys. But largely it was -- I was serving as a
2 consultant, really, in these cases. And then four of these
3 that I have been involved in have gone to some kind of
4 trial. The Neurochem v. Intech was a tribunal, not a trial,
5 and the Apotex v. Lilly was actually in Canada, a trial in
6 Canada.

7 Q. And in your service as an expert witness, have you
8 worked on the side of both the patent owner and the side of
9 the party being accused of infringement or challenging
10 validity of the patent?

11 A. Yes, only three of these actually had patent
12 litigations. The first one, I was with Rhone Poulenc, and
13 they were the patent owner. The last two, I was involved
14 with Apotex and Sandoz. And interestingly enough, Sandoz
15 you think of a major pharmaceutical company, but it was
16 actually not the patent holder in that case.

17 Q. And in some of these cases, have you testified at
18 trial in U.S. District Court?

19 A. Yes, in fact, in the first one, and I guess the last
20 one.

21 Q. And, Professor Martin, are you aware of any instances
22 where the Court did not accept you as an expert witness?

23 A. No.

24 MR. CAPUANO: Your Honor, Defendants offer
25 Professor Stephen Martin as an expert in organic and

1 medicinal chemistry, including the study of structure
2 activity relationships and the design and synthesis of
3 pharmaceutically active compounds, including analgesics.

4 THE COURT: Any objection?

5 MR. BEST: I guess I have some problem with the
6 "including analgesics," but I think the rest of that sounds
7 correct.

8 THE COURT: All right. Well, we're going to hear
9 from him today, and I'm sure he's going to cover all those
10 areas. I mean, he's talked about analgesics in his
11 background, and I don't know if there's anything else you
12 would like to elicit on that.

13 Is there any further development to your
14 objection?

15 MR. BEST: I think not at this time without
16 hearing the testimony.

17 THE COURT: All right. Well, we will be admitting
18 him as an expert. He is deemed an expert.

19 MR. CAPUANO: Thank you, Your Honor.

20 BY MR. CAPUANO:

21 Q. Professor Martin, in the course of your work on this
22 case, have you had a chance to review what we've been
23 calling the '593 patent?

24 A. I have.

25 Q. Okay. And do you have an understanding of when the

1 application was first filed for this patent?

2 A. I understand that -- yes, there's a priority date in
3 the foreign application which I recall was July 23rd, 1994.

4 Q. Okay. And have you provided opinions in this case
5 with respect to certain publications that are prior art to
6 the '593 patent?

7 A. I did.

8 Q. Okay. And do you have an understanding whether
9 there's a date that you can use to determine whether a
10 publication can be considered prior art to the '593 patent?

11 A. I do. It's my understanding that anything before that
12 filing date may be considered as prior art. I think there's
13 -- again, I'm not an attorney, but I think, I've been told
14 that there's a one-year window, like at least -- for --
15 beyond one year prior to the filing date, there really is no
16 controversy. Within that one year time frame just before
17 the filing date I understand there could be controversy or
18 could be discussion.

19 Q. Okay. And have you had a chance to review the claims
20 of the '593 patent?

21 A. Yes. There are many.

22 Q. Okay. Well, do you understand which claims have been
23 asserted against Actavis?

24 A. Oh, yes.

25 Q. Are those shown on the slide here?

1 A. Claim 8, Claim 61, Claim 117, and Claim 147.

2 Q. Okay. And with regard to Claim 8, do you see a
3 structure there as part of the claim --

4 A. I do.

5 Q. -- generic structure? Does that structure include
6 tapentadol hydrochloride?

7 A. Yes, it does.

8 Q. Okay. And Claim 61, do you have an understanding of
9 what the chemical compound is that's written in Claim 61?

10 A. Yes. I think that would be what we might refer to as
11 the IUPAC, I-U-P-A-C, those are all capital letters, name,
12 nomenclature for a compound that we refer to in these
13 proceedings as tapentadol. It's a lot easier to say.

14 Q. Okay. Is that --

15 A. Hydrochloride. Sorry.

16 Q. Thank you. Tapentadol hydrochloride?

17 A. Tapentadol hydrochloride.

18 Q. And what about Claim 117: Do you understand which
19 compound -- well, first of all, do you understand that Claim
20 117 is referring to a method? Do you see that?

21 A. Right, dependent claim I guess of compound 8, yes.

22 Q. And what is the method of Claim 8?

23 A. Well, the method of Claim 8 is a method of treating a
24 mammal suffering from pain, and said method comprising
25 administering to said animal an effective analgesic amount

1 of a compound of the general formula that they have depicted
2 there.

3 Q. And that general formula, I think you testified to,
4 encompasses tapentadol hydrochloride.

5 A. Correct. And then Claim 117 calls out tapentadol
6 hydrochloride specifically.

7 Q. And Claim 147 also asserted; do you have an
8 understanding of what the compound is that's written for
9 Claim 147?

10 A. I do.

11 Q. Okay, and what is that compound?

12 A. Well, this is, again, tapentadol, but it's -- in this
13 particular case, it's not limited to the hydrochloride salt.
14 It includes the hydrochloride salt or any pharmaceutically
15 acceptable salt.

16 Q. Okay, and you have a note here that this is subject to
17 December 4, 2012 Certificate of Correction. Do you see
18 that?

19 A. I do.

20 Q. Okay. Why do you have that there?

21 A. Well, I have that there because in the -- I can't
22 point, but there's an R --

23 Q. I got it.

24 A. You're pointing -- yes. This -- that R right there
25 doesn't make any sense, and so I think that is removed in

1 the correction.

2 Q. Okay. And with the correction, does this recite a
3 pharmaceutically acceptable salt of tapentadol?

4 A. Yes, it does, tapentadol, right.

5 Q. Okay. And in the course of your work in this case,
6 have you been asked to provide an opinion on whether these
7 four claims are valid or invalid?

8 A. I have.

9 Q. And have you considered whether in view of the prior
10 art as a whole these claims would have been obvious to a
11 person of ordinary skill in the art as of July 1994?

12 A. I have.

13 Q. Okay. And what opinion have you reached?

14 A. I have reached the opinion that they are obvious.

15 Q. And because they're obvious, does that give you a
16 further opinion whether they're valid or invalid?

17 A. I understand they're invalid because they are --
18 they're invalid for the purposes of a patent because they're
19 obvious.

20 Q. Okay. And in considering your opinions with respect
21 to obviousness, did you reach your opinions based on the
22 views of a person of ordinary skill in the art?

23 A. I did. It's my understanding that that is -- I guess
24 -- that's the lens, that's the perspective that you need to
25 take in order to determine whether a compound or an

1 invention is obvious.

2 Q. Okay. And have you provided here on Demonstrative
3 slide 8 your definition of a person of ordinary skill in the
4 art?

5 A. I have, and I believe this is lifted verbatim from my
6 opening report.

7 Q. Could you read it into the record, please?

8 A. Yes, sure. It says "Education and/or experience in a
9 field related to the design and synthesis of new analgesic
10 compounds, including the fields of organic chemistry,
11 medicinal chemistry and pharmacology, and knowledge of the
12 scientific literature concerning the same, specifically the
13 design and synthesis of organic compounds used for the
14 treatment of pain, including opioid analgesic and opioid
15 analogs for the treatment of pain as of July 1994."

16 And then I went on to say what the educational --
17 what I think the educational qualifications should be, and I
18 said that this in my opinion should be a person having a
19 Ph.D. with three to five years of experience in the design
20 and synthesis of analgesics, including opioid analgesics.

21 And I think also prior to this, given the -- this
22 person of ordinary skill would be working as part of a team
23 of expert people who knew something about pharmacology,
24 medicinal chemistry, structure activity relationships,
25 because this person would have to be able to understand and

1 communicate with these other individuals during the course
2 of this process.

3 Q. Do you have an understanding of what the level of
4 education was of the inventors on the '593 patent?

5 A. I believe they're all Ph.D.s. I know Dr. Buschmann
6 was a Ph.D. -- I know -- Dr. -- yes. I know it was
7 Dr. Buschmann because he got his Ph.D. in Aachen, as I
8 recall.

9 Q. Are you aware of the definition of the person of
10 ordinary skill in the art from one of Plaintiff's experts
11 that's different from yours?

12 A. Yes, I'm familiar with Professor Roush's definition.

13 Q. Okay, and how does Professor Roush's definition of a
14 person of ordinary skill in the art differ from yours?

15 A. You know, I don't remember the details and the
16 wording. I think if you compare his definition and my
17 definition, they're really -- they're equivalent except for
18 the one difference being what degree that person should
19 have. I think in his definition he believes one holding a
20 Bachelor's degree would qualify, and my definition is a
21 Ph.D.

22 Q. Okay. And whether the Court accepts your definition
23 or Professor Roush's deposition, would your opinions change
24 in this matter?

25 A. No, they wouldn't.

1 Q. Professor Martin, in considering whether the compound
2 claims that encompass tapentadol hydrochloride were obvious
3 to a person of ordinary skill in the art as of July 1994,
4 what kind of analysis did you perform?

5 A. Well, I did a lead compound analysis, and that's based
6 on what's written here that this proof of obviousness, in
7 order to prove obviousness based on structural similarity,
8 it requires that this person of ordinary skill would have
9 been motivated first to select a lead compound, and then
10 that person would have been I think motivated by prior art
11 literature references and so forth to modify that lead
12 compound, that prior art compound, and arrive at the claim
13 compound with the reasonable expectation of success that
14 this new compound would have either similar or improved
15 properties relative to the original lead.

16 Q. And do you have an understanding of whether as part of
17 a lead compound analysis there's a requirement that the
18 prior art directed a person of ordinary skill in the art to
19 just a single lead compound or whether multiple lead
20 compounds can be part of that analysis?

21 A. It's my understanding that there's no requirement that
22 this be a single lead compound. It's my understanding that
23 there's some legal case law or something like that that says
24 that that would be too restrictive a requirement.

25 Q. Okay. And this framework for analyzing obviousness

1 where first you consider what the prior art would suggest a
2 lead compound and suggest modifications to that lead
3 compound, one or more lead compounds, does that analysis
4 match up with the realities of how medicinal chemistry
5 groups design and develop new compounds?

6 A. Yes, I think so. I think we've sort of -- I sort of
7 explained this a little bit before, that you identify your
8 lead and then you start modifying that lead in ways that you
9 hope will improve it ultimately.

10 Q. And does this also match up with your experience in
11 designing new pharmaceutically active compounds?

12 A. Well, yes, it's certainly -- I mean, we've been
13 involved in a lot of structure activity relationships for
14 over 25 years in looking in great detail at interactions
15 between small molecules and proteins, and, yes, you make
16 incremental changes and you see what happens, and then you
17 use that information to then make subsequent changes.

18 Q. Okay. And now in terms of the steps a person of
19 ordinary skill in the art would take in 1994 to make a new
20 analgesic compound, have you summarized those steps?

21 A. Yes. I think so. I think first of all you have to
22 select the lead. You have to identify what your lead is.
23 And then you study the prior art to select the lead.

24 I think one of the important things that we do in
25 science is, we're constantly going back to the previous

1 literature, looking for precedent for things we like to do
2 and looking for knowledge that has been developed before us
3 in fields that or field situations, whatever, closely
4 related or as closely related as we can find them to what
5 we're trying to do.

6 Do you want me to go through all three of these
7 steps right now?

8 Q. Yes, let's go through all three of these and then
9 we'll take them one at a time.

10 A. All right. So first of all, we select this lead, and
11 in order to do that, we will study the prior art in a given
12 area. We will identify the pharmacophore of that lead
13 compound. I think the pharmacophore has been discussed
14 before, but let me just go through it again.

15 Essentially, a pharmacophore is -- these molecules
16 that we have that we're talking about are three-dimensional,
17 and these molecules have groups attached to them, and it's
18 these groups that interact with the receptors, the
19 biological targets that ultimately elicit the biological
20 response that you want.

21 And so there are two important -- well, a couple
22 of important things. One is what the nature of these groups
23 is, so the nature of those groups is important because they
24 interact with the protein, for example, and then their
25 arrangement, the three-dimensional arrangement in space is

1 important, because, for example, if you need to interact
2 this hand with this hand like this, it doesn't do you any
3 good if this is your molecule that won't interact with your
4 hand very well.

5 And so this pharmacophore is a combination of
6 shape, stereochemistry, three-dimensional orientation of
7 atoms in space, and different kinds of groups that are
8 arranged in space, and that are essential for -- and I
9 forgot -- that are essential for activity.

10 Q. And then the last of the iterative steps?

11 A. Right. And then so then it's modifying the lead
12 compound, so -- and we modify the lead compound in accord
13 with what we learned in step two here, and we start to make
14 changes in that lead that have precedent in the literature
15 first, that's what we do first, and then we move on to
16 making other changes, and each time we do this, as I said
17 before, it's an iterative process, and each time we make a
18 structural change, we evaluate the activity, in this case
19 analgesic activity, for example, see what the effect is, and
20 then we move on.

21 Q. Okay. Well, let's start at the beginning with
22 selecting a lead compound based on prior art.

23 And if you could, Professor Martin, I'd like you
24 to start at the beginning, take us back to the early 90's
25 and tell us how would a person of skill in the art in the

1 early 90's, before 1994, begin to consider what might be
2 lead compounds for developing a new analgesic.

3 A. Okay.

4 So as I said before, what they would do is, they
5 would familiarize themselves with all different kinds of
6 compounds that had analgesic activity. They would look at
7 properties, they would look at side effects, they would
8 consider in general all the things that were known about
9 those different compounds, and then they would make
10 judgments on what they thought might be a good starting
11 point.

12 Q. And so -- sorry. Go to the library, that would be the
13 first step, I guess?

14 A. Yes, you would go to the library. You know, these
15 days, we're a lot luckier than they were back in the 90's
16 and before. Nowadays you just walk up to your computer and
17 you go to Google and you type something in and you get more
18 information than you want. In science, there are special
19 search engines to find scientific information, but Google's
20 still pretty good for that.

21 But back in those days, I think people relied on
22 abstracting services and books, and certainly one of the
23 premier abstracting services in this general area would have
24 been Chemical Abstracts, and so that would probably have
25 been the historically the place that a person would have

1 relied on. And these abstracts are -- basically, they're
2 indexed, and you can just look up words like analgesic, and
3 you would find a bunch of references to analgesic agents.
4 And then as you went through this, you would find various
5 literature references, and then ultimately you would have
6 explored the field.

7 Q. Okay. And you've listed here what you referred to as
8 various possibilities among analgesics.

9 A. Yes. Certainly the first two, the opioids and the
10 NSAIDS, these are the ones that most people know about.
11 They're certainly the workhorses. Opioids are the
12 workhorses for severe pain. The NSAIDS are the workhorses
13 for not such severe pain.

14 Q. I'm sorry. Tell the Court, what is an NSAID?

15 A. Yes. NSAID -- thank you. NSAID is an acronym for
16 nonsteroidal antiinflammatory drug, and, the "S" is the
17 plural part.

18 Q. Go ahead. And are there NSAIDS that maybe lay people
19 would be familiar with?

20 A. Yes. I mean, aspirin is an NSAID. Tylenol,
21 acetaminophen is an NSAID. Ibuprofen, Aleev, those are all
22 NSAIDS.

23 And as far as opioids are concerned, morphine,
24 codone, hydrocodone, hydromorphone, there are a lot of
25 derivatives of morphine, opioid analgesics.

1 Q. And monoamine uptake inhibitors? What's a monoamine
2 uptake inhibitor?

3 A. Yes. So monoamine refers to the amines like
4 adrenalin, also known as epinephrine; noradrenaline, also
5 known as norepinephrine; serotonin. They're basically
6 aerial ethylamines. But these are neurotransmitters, and
7 compounds that have developed to inhibit their reuptake in
8 the synapses, which are part of the nerve, have been used to
9 treat a common -- one of the common treatments is
10 depression, attention deficit disorder, things like that.

11 But there are also -- I mean, you can go back
12 years. Clonidine is a monoamine uptake inhibitor, and it
13 was also used as an analgesic. Cannabinoids are another
14 possibility.

15 And then I come down to tramadol. Tramadol is
16 the only one of these that is -- well, it's not a single
17 compound. We'll I guess get to that.

18 But these other classes, the opioids, the
19 NSAIDS, monoamine uptake inhibitors, cannabinoids, these are
20 all groups of compounds, they're sort of generic classes,
21 whereas tramadol is a single compound -- well -- yes, it's
22 an enantiomeric mixture, but yes.

23 Q. So why have you listed certain classes of compounds
24 and then singled out one particular drug, tramadol, in this
25 list?

1 A. Well, the reason is is because of all of the
2 analgesics that a person of ordinary skill would find in
3 this search that we've just conducted, you would find all of
4 these compounds act by single mechanisms of action. The
5 opioids involve binding to opioid receptors. The NSAIDS
6 typically are cyclooxygenase inhibitors, so they have a
7 specific mode of action. Monoamine uptake inhibitors,
8 again, we've talked about those. Cannabinoids are generally
9 those compounds related to compounds found in marijuana.

10 Right. And so tramadol was unique amongst these
11 in that it had two modes of action. It had a dual
12 pharmacology, and it was a combination of opioid activity
13 and monoamine uptake activity.

14 Q. And in conducting your review of the prior art for
15 this case, did you identify any other analgesic that had a
16 dual mode of action that you just described, opioid plus
17 nonopioid mechanism of action that existed prior to 1994?

18 A. No, I didn't, and that's what made this particular
19 compound stand out. That's why I -- you look at that and
20 you say, this is different; this is special.

21 Q. And when you conducted your analysis for trying to
22 determine what a person of ordinary skill in the art would
23 select as a lead compound to develop new analgesics in 1994,
24 did you consider this landscape of known analgesics in
25 conducting your analysis?

1 A. Yes, I eventually came around to considering all of
2 these. I started with the opioids and the NSAIDS because
3 those are the ones that are obvious, and then as you
4 continue looking at these, you become aware of these other
5 possibilities.

6 Q. Did you have a chance to read the transcript of
7 Dr. Buschmann's testimony here in court last week?

8 A. Yes, I did. I had a chance to look through it.

9 Q. Did you read the part of his testimony where he agreed
10 that there was no other analgesic in the prior art with a
11 combination of activities that tramadol had?

12 A. I'm not sure he was that unequivocal. I think he may
13 have said something to the effect he was unaware of any. I
14 don't remember exactly what he said. But it was along the
15 lines of, yes, at least he was unaware of anything else. I
16 think he also -- I mean, I think in that testimony there was
17 a mention to Friderichs, I guess, and he had been asked, I
18 think, the same question, and he also didn't know of another
19 example.

20 Q. And are you aware of references that existed in the
21 prior art before 1994 that describe tramadol as unique and
22 atypical among analgesics?

23 A. Yes, I did.

24 Q. Okay.

25 MR. CAPUANO: Can we have Defendants' Exhibit 866,

1 please?

2 Q. Professor Martin, do you know what Defendants' Exhibit
3 866 is?

4 A. Yes. I think we referred to this as Raffa I, and it
5 was published in 1992, and it's a paper about the opioid or
6 nonopioid -- I'll read the title: "The opioid and nonopioid
7 components independently contribute to the mechanism of
8 action of tramadol, an 'atypical' opioid analgesic."

9 Q. So the word "atypical" is right in the title there?

10 A. Yes. Atypical, and italicized for emphasis -- well,
11 no, set off in quotes for emphasis.

12 Q. Is this a paper that you considered in rendering your
13 opinion in this case?

14 A. It is.

15 Q. And let's look at Exhibit page four, right-hand
16 column, just above "Antinociception test," and starting with
17 "The ability," and then going to the end.

18 Professor Martin, could you read this highlighted
19 portion into the record, please?

20 A. Yes. It says: "The ability of tramadol to inhibit
21 the neuronal uptake of monoamines in the same concentration
22 range at which it binds to Mu-opioid receptors is quite
23 distinct from the results for morphine or codeine and
24 clearly differentiate tramadol from these 'typical'
25 opioids."

1 Q. Okay.

2 MR. CAPUANO: And then, Ted, could you go to the
3 first page of the document, the bottom right-hand column,
4 and then that leads -- that continues onto the next page.

5 Thank you. Okay. And let's highlight sort of
6 from here to -- well, let's just take the highlighting off.

7 Q. Professor Martin, how does this paper, the Raffa I
8 prior art reference, inform your opinions about the dual
9 mechanism of action of tramadol?

10 A. Well, I mean, one of the things it says here, looking,
11 starting at the second line where it says "the clinical
12 experience," "the clinical experience has proven tramadol to
13 be unique among centrally acting strong analgesics." And so
14 that is, again, this word "unique" is now a word.

15 "Unlike typical opioid analgesics the therapeutic
16 use of tramadol has not been associated with clinically
17 significant side effects, such as respiratory depression,
18 constipation, or sedation," and it goes on further to say
19 "analgesic tolerance has not been a significant problem."

20 And I think if you -- let me just read a little
21 further.

22 Yes. The next part talks about psychological
23 dependence not being a problem, euphoria not being a
24 problem.

25 So I think the important message here is that

1 tramadol is unique, it has this dual mode of action, it's
2 got opioid and nonopioid mechanisms of action, and because
3 it has a dual mode of action, we can tone down how much we
4 use the opioid part of it for our analgesic effect because
5 we can use a combination of two different things, and
6 because we can tone down the opioid part of the equation, it
7 means that we don't have some of the side effects, at least
8 certainly not to the same degree as we have in the opioid
9 analgesics, and that's a big plus, because one of the huge
10 negatives of all of these opioids is, are there side
11 effects, and if you have a compound that certainly has
12 minimal or no side effects, no significant side effects, as
13 this passage says, that's pretty impressive. That's pretty
14 good.

15 Q. Okay. And with regard to combining these two modes of
16 action, on the one hand opioid action and on the other hand
17 nonopioid monoamine uptake inhibition action, have you put
18 together a little demonstration of how those things can be
19 combined to provide benefits?

20 A. I did. Is that the next slide?

21 Q. It is.

22 A. Yes, okay.

23 So here we have -- right. So we've got -- we
24 started off with the opioid and non-opioid, and in this
25 particular context, this nonopioid activity is again this

1 monoamine uptake inhibition, so we should probably be
2 specific about that. But again it has the reduced side
3 effects. So we started off -- we started off with -- yes.

4 I don't know why I can't get this pointer to work
5 over here.

6 Okay. We started off with opioid and non-opioid,
7 and we combine those two, and we get a compound with this
8 dual pharmacology, and that's got its advantages, as we've
9 seen, because of the reduced side effect profile of such
10 compounds. So that means you can use lower doses, hit the
11 opioid receptor in this particular case not quite so hard.
12 You're not relying on that mode of action solely to achieve
13 your analgesic effect.

14 Q. Okay. And you put this together to sort of illustrate
15 the idea?

16 A. I did. Yes, I did.

17 So another way of thinking about this is, we've
18 got cars, right? We've got cars that are gas -- have
19 gasoline engines --

20 Q. That's here on the left?

21 A. Right -- and cars that have electric engines, and then
22 we have the sort of hybrid of that car, which is the Prius,
23 and it has benefits. So the gas engine is polluting; it
24 gets bad mileage, it's noisy, at least sometimes. Electric
25 cars are quiet; electric cars get better mileage, electric

1 cars are nonpolluting. And so when you combine the two into
2 a single car, you get better fuel economy, less pollution,
3 and -- yes.

4 So there's a real advantage, and this is an easy
5 thing for a lot of people to understand, I think, about the
6 advantages of having something that has hybrid activity or
7 dual activity.

8 Q. Okay. And you mentioned before that tramadol is not a
9 single compound. Remember that?

10 A. I did.

11 Q. Okay. And so can you explain what is tramadol and in
12 particular discuss how it's a mixture?

13 A. Right. So tramadol is actually comprised of two
14 different compounds called enantiomers, the R,R enantiomer
15 here and the S,S enantiomer. These are two mirror-image
16 isomers.

17 Q. Let me stop you there and ask you to explain what that
18 is exactly, mirror image openings?

19 A. I was in here opening, and I don't know how much of
20 this has been explained, but mirror means isomers. What
21 this refers to is everything has a mirror image, except
22 vampires, I guess, that's what I tell my class, they don't
23 math mirror images. Everything has a mirror image, but the
24 question about isomerism is, are these different. And so in
25 this particular case, you can do your hands. And so you've

1 got your hands, and you can see if you imagine a plane
2 through these hands, these hands are mirror images. They
3 reflect one another.

4 The microphone is in the way.

5 They reflect one another, but they're not the same
6 because they're not superimposable. So if I try to
7 superimpose my hands, I can't. It's kind of like you can't
8 put a left-handed glove on a right hand.

9 So this particular way of viewing this, you have
10 to actually pick these molecules up and put them down on top
11 of each other like that. So enantiomers are mirror images,
12 but they're isomers, they're stereoisomers, which means they
13 have exactly the same items, the same functional groups, the
14 connectivity, everything is connected in exactly the same
15 way. The only difference is the way these atoms are
16 oriented in space.

17 Q. Okay. And with respect to tramadol, when a person
18 takes tramadol orally, what happens to this mixture?

19 A. Well, at least to some degree, and that degree varies
20 as I understand it with the individual who's taking the
21 drug, that is metabolized into what we call the metabolites,
22 which is these two compounds here, R,R ODMT I think is a
23 abbreviation for O-desmethyiltramadol, and S,S
24 O-desmethyiltramadol.

25 Q. When you say S,S, what does that mean?

1 A. The difference between --

2 Q. I can try to do it if you talk.

3 A. Okay. Sometimes this works.

4 THE COURT: If you want to get up, you can walk
5 around if it will make it easier to point at the screen
6 forward, that might be fine.

7 THE WITNESS: All right.

8 (The witness stepped down.)

9 Q. Professor, maybe over by the microphone.

10 A. Perhaps I should use your pointer.

11 Q. So we say this is metabolized, it's a desmethyl. So
12 this group here is a CH₃ group; it's a carbon atom with
13 three hydrogens attached to it. It's a derivative of
14 methane, and so it's the simplest hydrocarbon there is.
15 It's natural gas, methane.

16 And so what this group is called to when you take
17 one of the hydrogen atoms off and replace it with something
18 else, we have -- what is left is called a methyl group, and
19 that's abbreviated CH₃.

20 And so in going from this compound here, we have
21 this OCH₃ or this O-methyl, we go down here, and this methyl
22 group is replaced with a hydrogen atom, and so we refer to
23 that as desmethyl, so it's lost the methyl group.

24 Q. And how does that happen in the body?

25 A. Metabolically, there are a set of enzymes in the liver

1 called cytochrome P450 enzymes, and they're responsible for
2 these -- these demethylations and processes like that. And
3 there is a whole suite of these cytochrome P450s. Not
4 everyone has all of these P450 enzymes and not everyone has
5 them in the same amount, and so that's what makes metabolism
6 of these compounds different in different people.

7 Q. And so is it the case that some people can in their
8 body perform this metabolism better than others, or are
9 there even some people who can't have this conversion happen
10 in their body at all?

11 A. Yes. That was well known in the art at the time.

12 Q. And now with respect to the art and the prior art
13 before 1994, do you know whether these mixtures, the mixture
14 of tramadol isomers, the R,R and S,S enantiomers, that
15 mixture, and whether this mixture, the mixture of
16 metabolites, the R,R and S,S ODMT were studied as mixtures
17 and whether each of these four compounds had been studied
18 for activity?

19 A. Yes, they were. They were studied extensively --
20 well, quite extensively. We've got a number of references
21 that we'll go through, but yes, tramadol is -- the mixture
22 of enantiomers was studied as such, the mixture of
23 O-desmethyltramadol was studied, and then each of the
24 enantiomers of tramadol and O-desmethyltramadol was studied.

25 Q. So what do you have summarized here on this slide 17?

1 A. So this is some of the prior art that I looked at, and
2 certainly I looked at an awful lot of prior art, but these I
3 think are the ones that are most relevant to the case at
4 hand.

5 There's this 1978 paper by Flick, and we'll talk
6 about that more I think a lot later, but basically, he
7 looked at compounds that we could call racemic tramadol and
8 racemic O-desmethyiltramadol.

9 Frankus was one of Flick's contemporaries. They
10 published together. I think they were both on the original
11 tramadol panel. Frankus looked at tramadol, he looked at
12 the two isomers of tramadol, and he also studied a
13 diastereomer of tramadol, the so-called cis form of tramadol
14 which has a different arrangement of atoms in space than
15 tramadol itself.

16 Hennies is another person. He studied racemic
17 tramadol and racemic O-desmethyiltramadol.

18 Driessen, there are two papers by Driessen. In
19 one of them, he studied racemic tramadol, the two
20 enantiomers of tramadol, and racemic O-desmethyiltramadol.

21 Driessen in the second one studied racemic
22 tramadol, racemic O-desmethyiltramadol, and their
23 enantiomers.

24 Raffa, racemic tramadol; Raffa, the second
25 reference to Raffa, racemic tramadol and the two enantiomers

1 of tramadol.

2 And then Sevcik studied the enantiomers, the
3 individual enantiomers of the four different compounds.

4 So there's quite a lot of prior art related to the
5 properties of these molecules in combination and
6 individually.

7 Q. Okay. And we already looked at Raffa I, so maybe
8 let's start with one of the orders.

9 MR. CAPUANO: Can I have Defendants' Exhibit 691?

10 Q. Do you recognize what's been marked as Defendants'
11 Exhibit 691, Professor Martin?

12 A. I do. It's a paper by Hennies. I think the date of
13 this was '88. I think I just have it on the previous slide.
14 It doesn't say it here. But it's a paper -- right, 1988.
15 It's a paper about receptor binding analgesic and
16 antitussive potency of tramadol and other selected opioids.

17 Q. Okay, and let's go to the second page of the document,
18 the upper right-hand corner. There's some structures up
19 there.

20 Professor Martin, what's being studied in this
21 paper? What are these different structures?

22 A. So this study was I think intended as a pairwise
23 study, but you can compare all these compounds, and what
24 they were doing was trying to find out what the effect of
25 the difference was between compounds with this O methyl

1 group and compounds with the OH group.

2 So if you look over here, there's this R group on
3 this ring system, and you see the R group down here, you see
4 an R group down here. Organic chemists lots of times when
5 they're going to look at a series of compounds and they're
6 going to be replacing a substituent in a particular position
7 will oftentimes use the designation of R as sort of a
8 generic substituent, and then they to the side in some way
9 tell you what those substituents are.

10 So in each of these cases, R is OH and OCH₃.

11 This compound is morphine.

12 Q. Sorry. The one with R equals OH?

13 A. Right, and it's codeine, that's R equals OCH₃.

14 This molecule here, which differs from morphine
15 in that we don't have -- this is a representation of a
16 carbon-carbon double bond. This is an unsaturation, so the
17 difference between these two molecules is essentially
18 hydrogen, H₂, and then at the bottom is O-desmethyltramadol
19 and tramadol.

20 So they were comparing the effect of having the OH
21 versus the OCH₃, which is better.

22 Q. And in going from the top structures, morphine and
23 codeine, and moving on down, how do these compounds relate
24 to each other in terms of structure as opioids?

25 A. Well, they're all opioids. They all have opioid

1 activity. Morphine, of course, is the natural occurring
2 compound. I don't know that hydromorphone occurs naturally.
3 I don't know. But this is the parent sort of opioid
4 analgesic.

5 And in the history of studying opioids, there's a
6 long tradition in the area to try -- of people trying to
7 improve on the activity of morphine; that is, what they're
8 trying to do is find a way to keep the analgesic activity
9 but get rid of some of the side effects. And so what they
10 did -- there's many, many references to people doing this --
11 they start simplifying the structure of morphine, and you
12 can go all the way down to tramadol to find it, but
13 basically what people did is they would remove atoms from
14 morphine, they would remove rings from morphine, they would
15 cleave bonds in morphine, and they would look at things, and
16 ultimately, if you look at tramadol down here and
17 O-desmethyiltramadol, the way they've drawn it, we can see
18 how this structure relates to the structures above. This
19 ring here, is this ring, and this ring; this ring over here
20 we'll call a cyclohexane ring because that's what we call
21 it. It's a six-membered ring, it's saturated. You see that
22 cyclohexane ring here, and you see that cyclohexane ring
23 here in morphine, although it has this carbon-carbon double
24 bond.

25 And then you look at this carbon atom here in all

1 of these compounds, and this carbon atom in each case has
2 got four different substituents. And so here the
3 substituent is oxygen; here, the substituent is a carbon
4 atom; here, the substituent is a carbon atom. A lot of
5 similarities. And then finally --

6 Q. And just let me -- sorry to interrupt.

7 Each of these intersections in organic chemistry,
8 does that represent a carbon atom?

9 A. Yes, it is.

10 Q. Okay.

11 A. Okay.

12 Q. All right. Go ahead.

13 A. And then finally, we have this amino group. This is
14 the nitrogen, so this happens to be what we call an amino
15 group, it's a functional group, and this amino group in this
16 particular case has two methyl groups, but the important
17 thing here is this nitrogen atom is attached to three
18 different carbons, okay? These two carbons are the same,
19 they're methyl groups, but this one is different. So this
20 nitrogen is attached to three different Cs, so this is a
21 carbon atom here, too, and you see the arrangement. This
22 connectivity here in tramadol is the same as what you have
23 up here, and the same as in morphine.

24 So there are a lot of structural similarities is
25 what --

1 Q. And in each case, are the compounds similar with
2 respect to the number of carbon atoms separating the
3 nitrogen atom in the phenyl ring?

4 A. Right. So in each case, I think -- it's a little hard
5 for me to see here -- here. It's easy, there's one, two,
6 three carbon atoms that separate this amino group from the
7 aromatic ring. It's a little harder to count here -- one,
8 two, three -- so there's three atoms, three carbon atoms
9 between the nitrogen atom and the aromatic ring in all of
10 these compounds.

11 Q. So in a way, is tramadol -- looking at morphine is
12 kind of a stripped-down version of morphine, a simplified
13 version of morphine?

14 A. Yes, it.

15 Q. And that's a -- I think you testified -- is that a
16 common approach to developing analgesics?

17 A. Yes, it certainly is in the opioid area. And Flick,
18 which we didn't discuss yet, even comments on this.

19 Q. Okay. And so just so we understand what's being
20 studied with respect to tramadol, they're going to compare
21 tramadol as a mixture of S,S and R,R isomers, right,
22 enantiomers --

23 A. Yes.

24 Q. -- with O-desmethyltramadol, that same mixture that we
25 looked at two slides ago; right?

1 A. That's correct.

2 MR. CAPUANO: Okay. So let me have, on that same
3 page, Ted, at the bottom there, there's Table I.

4 I need the whole row. Yes.

5 Q. Professor Martin, what's being presented in Table 1
6 here with respect to a comparison between tramadol mixture
7 of enantiomers and the O-desmethylntramadol mixture of
8 enantiomers where the methyl group has been replaced with
9 hydrogen?

10 A. Essentially, what they're doing here in layman's terms
11 is looking at potency of O-desmethylntramadol and tramadol,
12 and they're binding to various opioid receptors. In other
13 words, how good are they? And in these cases, the smaller
14 the number, the better it is. And so if you look across
15 this column, you can see that the O-desmethylntramadol wins
16 every time. Sometimes it wins bigger than other times, but
17 it's always -- it's always better than the -- the
18 O-desmethylntramadol is always better than tramadol.

19 Q. Okay. And so just to clarify here, in the first
20 column, 4.4 times 10 to the minus seven is less than 1 .710
21 times to the minus six; correct?

22 A. Right. It's about one fourth or something -- one
23 third.

24 Q. And going across, in each case, is every reported
25 value for IC50 for the O-desmethyl less than the reported

1 value for tramadol?

2 A. Yes, the average values that they're reporting here
3 are -- we could talk about these -- these overlapping
4 numbers, these ranges, but I think that -- one of the main
5 interests here was on analgesic activity, and that would be
6 Mu-opioid, so that makes this column, at least from the
7 standpoint of opioid analgesic activity, that makes this
8 column here the most important. So here, there's a more
9 significant difference.

10 Q. Now, with respect to tramadol, what does this data
11 tell you about the relative importance of the OCH3 group in
12 tramadol and the OH group in desmethyltramadol for analgesic
13 effect?

14 A. Well, it tells you, and I think it's written in the
15 abstract or the summary for this paper is that the hydroxy
16 compounds are more potent than the methoxy. So those OH
17 compounds are more potent than the OCH3 compounds.

18 MR. CAPUANO: Okay. And, sorry, Ted, just the
19 summary on DTX 691, the beginning of the summary, first
20 page. Here.

21 Q. Is this the language you were talking about, Professor
22 Martin, starting with "The influence?"

23 A. Yes, so there's the influence. I think it's a little
24 further down.

25 So there, where it says "All three hydroxy

1 compounds had higher opioid receptor affinities than the
2 corresponding methoxy derivatives and were more active at
3 the Mu-site," the Mu-opioid side site.

4 Q. Okay. So what's the take-home message with respect to
5 this reference and your opinions with respect to the
6 relative analgesic potency of tramadol versus
7 O-desmethyltramadol?

8 A. Well, we haven't really looked at the table that
9 speaks to the analgesic activity, I don't think, have we?

10 Q. All right. Let's look at Table 2.

11 A. To answer your question.

12 Q. What's being presented in Table 2, and how does the
13 data in Table 2 inform your opinion?

14 A. Okay. So in Table 2 here, if we look at Column 1, we
15 see the names of the compounds that were tested, and in
16 Column 2, we see the analgesic effect, and this is an
17 effective dose -- the ED50, and so an ED50 is the dose at
18 which half of the animals exhibit the effect that you're
19 looking for. So some level of analgesic effect.

20 And so the smaller the number, the better. And so
21 desmethyltramadol is almost three whereas tramadol is almost
22 nine. You see O-desmethyl isn't much weaker than morphine,
23 actually. So it's -- but basically, the message here is
24 O-desmethyl is a better analgesic than tramadol, and that's
25 the take-home.

1 Q. Okay. Well, let's look at one of the other papers on
2 your list.

3 MR. CAPUANO: Let's go back to the slides.

4 Q. Let's look at the Driessen I paper, 1992. It's
5 Defendants' Exhibit 758.

6 Professor Martin, do you recognize what's been
7 marked as Defendants' Exhibit 758, and what is it?

8 A. I do. This is a paper, as you said, we referred to as
9 Driessen I. It was published in 1992, and it was a paper
10 that studied the interaction of the analgesic agent tramadol
11 with the uptake and release of 5-hydroxytryptamine in the
12 rat brain, five hydroxytryptamine would be known to lay
13 people as serotonin. So we can use serotonin, I think,
14 probably easier.

15 MR. CAPUANO: Ted, could you put page one, on the
16 right-hand column, could you blow that up for us please?

17 Q. Could you summarize, Professor Martin, the key finding
18 from this paper as reflected in Table 1?

19 A. Well, I think, you know, the most important finding in
20 this table that informs an opinion of what might ultimately
21 turn out to be a good lead compound is the fact that
22 O-desmethyltramadol has the weakest affinity for this
23 serotonin reuptake mechanism; tramadol itself and the plus
24 enantiomer about the same, three and two, roughly, whereas
25 the tramadol enantiomer is somewhat weaker, but still more

1 potent than the O-desmethyiltramadol tramadol. So it's
2 perhaps important to point out that this O-desmethyiltramadol
3 is the racemate, it's not the single compound, it's a
4 mixture of the two enantiomers, the R,R and the S,S.

5 But I think normally people are trying to avoid
6 serotonin activity, and one of the reasons is is that a lot
7 of compounds that bind to serotonin receptors have
8 hallucinogenic psychometric results. LSD, for example, is a
9 mimic of serotonin that is better than serotonin, mescaline,
10 these drugs of abuse, that are bad.

11 Q. And with respect to binding to the serotonin receptor,
12 which you mentioned is related to these side effects, how
13 does the O-desmethyiltramadol compare with either the
14 tramadol mixture or either of the tramadol enantiomers with
15 respect to IC50 and binding?

16 A. Well, it has a weaker effect at that -- that serotonin
17 reuptake.

18 Q. And with respect to what you might consider a lead
19 compound, how does this data lead a person of ordinary skill
20 in the art to -- well, how does this paper inform a person
21 of ordinary skill in the art when trying to select the lead?

22 A. As I said, what this would tell someone of skill in
23 the art is that O-desmethyiltramadol had weaker interactions
24 with the serotonin reuptake and so would likely have fewer
25 serotonin-related side effects associated with it.

1 Q. Okay. Let's look at one of the other papers. Let's
2 go back to the slide.

3 Let's look at Driessen II, 1992 paper. It's
4 Defendants' Exhibit 694.

5 Professor Martin, do you recognize Defendants'
6 Exhibit 694, and what is it?

7 A. Yes. This is another paper by Driessen. Driessen was
8 studying the other mode of action in this series of papers.
9 He recognized that these compounds were opioids, and he was
10 studying this non-opioid contribution to the analgesic
11 effect. So this was published in 1993, and essentially now
12 he's looking at the effects of tramadol on norepinephrine
13 reuptake.

14 Q. Okay. Let's put up Table 2 on Exhibit page four,
15 right-hand column at the top.

16 Professor Martin, what does this tell you about
17 the substances that were tested in this paper in terms of
18 whether they were mixtures or individual tramadol and
19 O-desmethyiltramadol enantiomers?

20 A. Well, so in this paper, we're studying everything.
21 We're studying tramadol --

22 Q. Mixture ?

23 A. The mixture, we're studying O-desmethyiltramadol as a
24 mixture, and we're studying each of the individual
25 enantiomers of tramadol and each of the individual

1 enantiomers of O-desmethyltramadol.

2 Q. Okay. And here, is this reporting on binding to the
3 noradrenaline receptor?

4 A. Yes. Basically what they're looking at is how -- how
5 potent are these compounds at releasing norepinephrine.

6 Q. Which is a reflection of how strongly they're binding
7 to the receptor?

8 A. Well --

9 Q. Go ahead.

10 A. It's not a simple question like that. I think what
11 we're looking for is how they interact with this reuptake
12 system, and it's a little more complicated than just a
13 receptor. But yes, a receptor is involved.

14 And so I think the lesson to be taken from this is
15 that the minus enantiomers seem to be the best. So minus
16 tramadol is 1.6, so it's roughly twice as good as the
17 mixture of tramadol, and the minus enantiomer of
18 O-desmethyltramadol is about the same potency. So both of
19 those are very potent in this system and about the same.

20 Q. So as compared to the plus enantiomer of tramadol, the
21 minus enantiomer is more potent in this assay; is that the
22 conclusion?

23 A. Correct.

24 Q. And with respect to the O-desmethyltramadol metabolite
25 mixture, the minus enantiomer is more potent than the plus

1 enantiomer; is that --

2 A. Yes, that's correct.

3 Q. -- what the data show?

4 A. Right. And the minus enantiomer is also more potent
5 than the mixture.

6 Q. And how does this data inform a person of ordinary
7 skill in the art about selecting a lead compound among this
8 mixture -- of mixtures and individual compounds?

9 A. So these data suggest that if you were to select
10 things, like I said at the beginning, the minus enantiomers
11 look to be -- well, they are the more potent -- the more
12 potent compounds in this assay, and they're comparable. And
13 so each one of these prior art references, we're looking at,
14 you know, what is the lesson learned and what is the potency
15 and so forth and so on. And so at the end, you kind of put
16 all of that together and say, okay, so which is going to be
17 my best -- my best starting point.

18 Q. Okay, and these are all references that existed in the
19 literature prior to the filing date of the Buschmann; right?

20 A. Yes, and I think all of these references are
21 Grunenthal references, too. They're from, within that
22 company.

23 Q. Okay. Let's look at the next paper. This will be the
24 Raffa II paper, 1993 Raffa II paper, Defendants' Exhibit
25 733.

1 And do you recognize what's been marked as
2 Defendants' Exhibit 733, Professor Martin, and what is it?

3 A. I do. It's, as you represented, it's the Raffa II
4 manuscript -- paper, sorry. It was published in 1993, it
5 looks like, and it was a "Study on the complementary and
6 synergistic antinociceptive interaction between the
7 enantiomers of tramadol."

8 MR. CAPUANO: Okay. Ted, if you could put the
9 abstract at the top of the screen and then Table 1 and
10 Exhibit page four at the bottom of the screen.

11 Q. Okay. Professor Martin, take us through the data.

12 MR. CAPUANO: And also, Ted, if you could
13 highlight here on the left-hand side of the abstract,
14 starting with the plus enantiomer K1 values, and down to
15 here. Maybe blow that up, and just pull it up a little bit
16 so we can see the top of the table. There you go. Good
17 enough. Thank you.

18 Q. Professor Martin, can you summarize the key findings
19 from this data and this paper as they relate to your opinion
20 regarding selection of a lead compound by 1994 for further
21 development of an analgesic?

22 A. Yes. I mean, in words, it summarizes -- the key
23 points are summarized in the abstract, but I think in this
24 particular case, I think it's easier to look at the table
25 and figure out what's going on.

1 So we're comparing tramadol as the racemate, as
2 the mixture, and we've got the two individual enantiomers,
3 and we're looking at how well these different compounds
4 interact with different receptors. And so there's a Mu
5 receptor that's a Mu-opioid receptor. There's the delta and
6 kappa which for all intents and purposes aren't very
7 important here, and then there's the NE, that's the
8 norepinephrine receptor, and then the 5-HT, which is the
9 serotonin receptor.

10 And so again, in this table, lower is better, and
11 so you can see from the binding at the Mu-opioid receptor
12 the plus tramadol is much better than minus tramadol, and
13 there's not a whole lot of difference between tramadol and
14 minus tramadol -- and plus tramadol, not even a factor of
15 two.

16 And then if you look at -- under the NE column,
17 you see that minus tramadol has its greatest effect, has the
18 greatest effect at the norepinephrine receptor --

19 Q. And again, lower numbers mean?

20 A. Minus is better, right, lower number is better.

21 And then if we go to the serotonin receptor, it's
22 plus tramadol that has the best affinity.

23 Q. Okay, and that serotonin affinity, that's the affinity
24 that is related to the serotonin side effects that you
25 talked about.

1 A. Right. Right. Right. And so it is the most potent
2 binder, that serotonin receptor.

3 Q. Go ahead. Sorry.

4 A. Well, I guess the next thing is, what do I conclude
5 from this?

6 So, you know, plus tramadol -- I mean, minus
7 tramadol it looks like has very little Mu-opioid activity,
8 so it's certainly not going to have a lot of analgesic
9 effect associated with its binding at that site. The
10 analgesic effect it does have will result from its
11 interaction with norepinephrine.

12 Plus tramadol on the other hand I would say has
13 significant affinity for all three of these. The Mu-opioid
14 receptor is the best of the three.

15 At the norepinephrine, it's weak, but not
16 insignificant.

17 And then at the serotonin receptor, of course,
18 we said it's the best.

19 And so there's kind of a balance here. When I
20 say it's -- the norepinephrine affinity is not bad for it,
21 it's comparable to the Mu affinity of the tramadol mixture.
22 So it's 2.1 versus 2.5, so it's very similar.

23 So really, plus tramadol has not dual mode of
24 action, perhaps; it has maybe triple mode of action, with
25 serotonin being maybe the one you don't want. But it's got

1 a triple mode of action.

2 Q. Okay.

3 A. So maybe -- it's the one that has perhaps the best
4 balance amongst these different receptor activities.

5 Q. Let's go back to the slide.

6 Okay. And then let's look at the final paper you
7 have listed here, the Sevcik 1993 paper, Defendants' Exhibit
8 736.

9 Do you recognize Defendants' Exhibit 736,
10 Professor Martin, and what is it?

11 A. Right. This is a paper by Sevcik, published in 1993,
12 and it's a study of the "Effects of the central analgesic
13 tramadol and its main metabolite, O-desmethyiltramadol, on
14 rat locus coeruleus neurons." The locus coeruleus is the part
15 of the brain that senses nociceptive pain, so it's relevant
16 to the analgesic effect we're trying to find, to study.

17 Q. And let's look at summary point four.

18 Okay. So try to explain to us, what's going on in
19 these experiments? How are these experiments being
20 conducted and what substances are being tested?

21 A. So to the question of what substances are being
22 studied, you see that plus -- sorry, minus tramadol is being
23 studied. Here's plus O-desmethyiltramadol being studied.
24 Here's plus tramadol being studied, and here's minus
25 O-desmethyl. So this is the study of the individual

1 enantiomers.

2 Q. Okay.

3 A. And the other two compounds that are listed here,
4 well, actually, naloxone -- yes, naloxone and rauwolscine,
5 these are antagonists. So naloxone is a opioid antagonist,
6 and I'll explain this a bit more in a second, and
7 rauwolscine is a norepinephrine antagonist.

8 And so what they were looking at was what is the
9 mode of action of these different enantiomers. Are they
10 single, do they interact with the norepinephrine, the
11 opioid, or both.

12 Q. And by introducing either rauwolscine or naloxone or
13 both, are they able to determine which of the actions each
14 of these individual compounds has?

15 A. Correct, and so they determine that minus tramadol,
16 because of the effect of rauwolscine, is primarily
17 interacting with the alpha two adrenergic receptor, which is
18 the norepinephrine one.

19 Q. Because the presence of rauwolscine turns off the
20 action?

21 A. It turns off the action, right. It's an antagonist.
22 It turns off the action of the minus tramadol.

23 And then plus tramadol is an opioid, because its
24 action is turned off by Naloxone, which is an opioid
25 antagonist. But in the case of plus tramadol and minus

1 O-desmethyiltramadol, you needed both of these in order to
2 wipe out the analgesic activity. So that experiment tells
3 you that tramadol and O-desmethyiltramadol act by two modes
4 of action, and those modes of action are the opioid and
5 norepinephrine pathways.

6 Q. Okay. So let's go to point eight in the summary, and
7 is that what -- can you explain how this relates to the
8 summary that you just gave?

9 A. Yes, I just said that.

10 (Laughter)

11 A. Do you want me to read it?

12 Q. No, it's in the Exhibit.

13 A. And I think the important thing here is, since we
14 started talking about dual mode of action, what we know at
15 this point fairly conclusively is that two of these
16 compounds, two of these individual compounds, the plus
17 tramadol and the minus O-desmethyiltramadol, have a combined
18 mode of action relating to Mu-opioid and norepinephrine
19 reuptake. Or the alpha two adrenergic.

20 Q. Okay. So in reviewing these papers that studied the
21 various mixtures of tramadol isomers, mixtures of
22 O-desmethyiltramadol isomers, and each individual component,
23 are there take-home messages for these four papers?

24 A. Yes. Yes.

25 Q. And can you go through them?

1 A. If I can remember these exactly.

2 So we haven't really talked much about Flick or
3 Frankus, but Hennies essentially informed us that the
4 hydroxy compound O-desmethyltramadol was about threefold
5 more potent than tramadol itself. And then these are the
6 mixtures, these are the racemates, these are the mixtures
7 and enantiomers.

8 Driessen, he studied the serotonin aspects, you
9 know, the extent to which these compounds interacted with
10 the serotonin reuptake system or receptor, and what he found
11 is that -- let's see -- that the tramadol and its two
12 enantiomers are I would say reasonably potent, but the
13 racemic O-desmethyltramadol tramadol was not very potent
14 against that receptor, so it had weak activity.

15 And Driessen II, we studied the norepinephrine
16 reuptake system, and we found the lesson there was the minus
17 enantiomers are the better ones.

18 And Raffa III -- II, sorry, we studied -- we found
19 out that the plus isomer of tramadol is probably the better
20 of the three possibilities.

21 And in Sevcik, we learned that plus tramadol and
22 O-desmethyltramadol are -- plus tramadol and minus
23 O-desmethyltramadol have a dual mode of action.

24 There's another conclusion that we didn't talk
25 about that I think is important and formed my opinion, and

1 that is that -- if we could look at the summary bullets
2 again, there was a point in there where -- actually, I
3 didn't comment on it, in that first bullet that you showed?
4 It suggests that the -- we're looking at that exhibit --

5 Q. From Sevcik?

6 A. The Sevcik paper.

7 Q. Okay. Let's bring back up Sevcik, Exhibit 736.

8 A. Something I forgot to mention because I realized I was
9 maybe getting longwinded on my explanation. I'm sorry.

10 No, it's not that one.

11 Go to four.

12 Right.

13 So there is certainly the suggestion here in this
14 last sentence that O-desmethyltramadol is three times more
15 potent than tramadol itself because the concentration they
16 use for tramadol is three times what the concentration they
17 use for O-desmethyl to see the same effects.

18 Q. And when you say tramadol, you mean plus tramadol?

19 A. I'm sorry. Plus tramadol and minus
20 O-desmethyltramadol. So minus O-desmethyl looks like it may
21 be three times more potent than plus tramadol.

22 Q. Okay. So let's go back to the slides, and putting
23 this all together now after your review of the prior art,
24 and considering the body of literature that existed prior to
25 July 1994 for tramadol and its metabolite and its mixtures

1 and enantiomers, what would a person of ordinary skill in
2 the art select as a lead compound for developing an improved
3 analgesic?

4 A. Well, let's take this stepwise.

5 I think initially our goal was to find something
6 with the dual mode of action. That was what tramadol --
7 that's what got our attention at the beginning. And so we
8 learned that only two of these have that dual mode of
9 action. Maybe R,R has three, R,R and tramadol may have
10 three. So these are the two that have that dual mode of
11 action.

12 Of these two, our analysis, my analysis of the
13 prior art says that this S,S O-desmethyltramadol is the
14 better of the two. It has, as I said a minute ago, the dual
15 mode of action. There's no metabolism that's necessary, so
16 people without enough cytochrome P450 enzymes can use this
17 drug, we don't have to rely on metabolism.

18 Q. That's because the methyl group is already off; right?

19 A. The methyl group is already off.

20 It's more active than R,R tramadol.

21 Q. I'm sorry, which is the other compound --

22 A. Which is tramadol, the other compound -- it
23 disappeared. But the other compound with dual mode of
24 actions.

25 And it has low serotonin activity.

1 So for those four reasons, this would be the most
2 promising of all of them.

3 Q. And in arriving at your conclusion about what the lead
4 compound would be for that person of ordinary skill in the
5 art at the time, in 1994, did you consider anything that
6 wasn't -- did you consider anything that was published on or
7 after July 1994?

8 A. No.

9 Q. Did you look at the '593 patent in arriving at your
10 conclusion with regard to what the lead compound would be?

11 A. No.

12 Q. Did you look at any Grunenthal documents to arrive at
13 your conclusion about what the lead compound would be?

14 A. No. This was all an analysis in my opening report,
15 and it was all absent any information from Plaintiff.

16 Q. And nevertheless, are you aware that Plaintiffs have
17 criticized your selection of the lead compound as being
18 driven by hindsight?

19 A. I am.

20 Q. And what is your understanding of Plaintiffs'
21 criticism of your lead compound analysis?

22 A. I don't understand it.

23 Q. Well, do you understand what they're criticizing you
24 of doing?

25 A. Well, yes, I think what they're criticizing me of

1 doing is starting with tapentadol and working my way back to
2 tramadol.

3 Q. And was tapentadol described in any of the papers that
4 you considered and relied on for your opinion about what
5 would be a lead compound?

6 A. No, tramadol -- I'm sorry, tapentadol wasn't known at
7 the time.

8 Q. And so do you agree with Plaintiffs' criticism that
9 you worked backwards from tapentadol with perfect hindsight
10 and arrived at this compound as your lead compound?

11 A. No, I don't agree at all.

12 MR. CAPUANO: Okay. Your Honor, we're going to go
13 to the next of the three steps, and if we're looking for a
14 break, this might be a good time.

15 THE COURT: I think that sounds like a perfect
16 time.

17 All right. Let's take a few minutes for a break.

18 I will tell the witness that you may be released
19 from the stand right now, but you remain under oath, and
20 since you still are testifying, you cannot talk to your
21 counsel about your testimony.

22 And everyone else can take a break, stretch out a
23 little bit, and we'll come back and revisit the issue.

24 All right. Thank you very much.

25 THE COURT CLERK: All rise.

1 (Recess taken)

2 THE COURT CLERK: All rise.

3 THE COURT: All right. Everyone, have a seat.

4 The witness resumed the stand.)

5 THE COURT: We got a little longer break. Sorry
6 about that. I was attending to a couple of things.

7 So let's begin. Thank you.

8 Any estimate as to the time for this witness?

9 MR. CAPUANO: We've got a ways to go, maybe at
10 least another half.

11 THE COURT: A half. Okay.

12 MR. CAPUANO: At least another half.

13 THE COURT: At least another half.

14 And what are we thinking in terms of cross? Any
15 kind of estimate?

16 MR. BEST: My guess is sort of hour to an hour and
17 a half.

18 THE COURT: All right. So it sounds like he may
19 not be finished tonight, then. All right. And he's
20 prepared to come back tomorrow?

21 All right. So let's keep going and see how much
22 ground we cover. Thank you.

23 MR. CAPUANO: Thank you, Your Honor.

24 BY MR. CAPUANO:

25 Q. Professor Martin, you had indicated a sort of

1 three-step process that you went through, and we've looked
2 at the first step, which was selecting a lead compound, and
3 now let's turn to the second step that you've identified
4 here which is "identify pharmacophore of lead compound,
5 study prior art to learn SAR."

6 So having arrived at a lead compound, what would
7 be the next step a person of ordinary skill in the art would
8 take in developing a new and improved analgesic starting
9 with tramadol for in particular minus O-desmethyiltramadol?

10 A. Okay. So as the bullet says, we need to essentially
11 study the prior art and what the prior art says about
12 structure activity relationships for this lead compound to
13 the extent we find information, and as I said earlier, part
14 of this will be to identify the pharmacophore, that is, the
15 part of the molecule that's essential for biological
16 activity.

17 Q. Okay.

18 THE COURT: And also, I just want to remind the
19 witness, but you remain under oath, sir, so we're not
20 re-swearing you in. All right?

21 THE WITNESS: Okay. Thank you.

22 THE COURT: Thank you.

23 Go ahead.

24 BY MR. CAPUANO:

25 Q. And Professor Martin, was there any prior art

1 available before 1994 that would have informed a person of
2 ordinary skill in the art to determine the pharmacophore for
3 tramadol, in particular minus O-desmethyiltramadol?

4 A. Yes, there was.

5 MR. CAPUANO: Okay. And let's have first
6 Defendants' Exhibit 715. The next page.

7 Q. Professor Martin, do you recognize what's been marked
8 as Defendants' Exhibit 715?

9 A. Yes. This is the German version of a paper by Flick.
10 I think this was published in 1978. My German pronunciation
11 is not very good anymore, but perhaps we could have the
12 English version.

13 MR. CAPUANO: Yes, let's have the English version.
14 Actually let's have Exhibit -- and I mentioned this before
15 when Dr. Buschmann was on the stand. Deposition Exhibit 108
16 from Professor Roush is the best photocopy we have of the
17 English translation.

18 No, it's in Exhibit 108 from the Roush deposition.

19 I believe the English translation is in the prior
20 art binder, and it's also included with the binders we
21 handed out.

22 This was used in the cross-exam with
23 Dr. Buschmann, if that's helpful, Ted.

24 Well, let's use the ELMO, Your Honor, if that's
25 acceptable.

1 THE COURT: That's fine. Yes, that's fine.

2 MR. CAPUANO: We've got a lot of this summarized
3 on slides.

4 Q. Okay. Well, this has some of my highlighting on it,
5 so we won't use all of it.

6 Q. Professor Martin, do you recognize the document that's
7 shown here on the screen?

8 A. Yes, this is the English translation of that article
9 that you just had up, "Studies on the chemical structure and
10 the analgesic activity of phenyl-substituted
11 aminomethylcyclohexanols," and so these phenyl substitute
12 aminoclohexanols are compounds that have the structure of
13 tramadol, so essentially this is one of the things I
14 referred to earlier. It's a study of structure activity
15 relationships.

16 MR. CAPUANO: Okay. And just go to the slides,
17 Ted. I think that would probably be the easiest thing to
18 do.

19 Q. Professor Martin, you've reviewed the Flick 1978 paper
20 as part of your work in this case; is that right?

21 A. I have.

22 Q. Okay. And can you explain for the Court how -- well,
23 what the Flick paper presents in terms of structure activity
24 relationships for these compounds?

25 A. Right. Well, it presents a number of aspects of the

1 structure activity relationships, and so what he's looking
2 at specifically is how changes in structure affect analgesic
3 activity.

4 And this particular slide, and in this particular
5 slide what he's looking at is basically the effects of
6 changing the substitution on this nitrogen atom here.

7 MR. CAPUANO: Can you blow this up a little bit
8 here?

9 Oh, it's a PowerPoint, so you can't.

10 A. So he's looking at changes of these R groups, which
11 are these R groups here. From memory, I think they're 3 and
12 4.

13 Q. Okay. So there are two groups on this nitrogen 1
14 labeled R3 and one labeled R4; is that right?

15 A. That's correct.

16 Q. Going back, and I apologize, groups on the nitrogen
17 atom there, how does this table relate to changes in those
18 groups?

19 A. Okay. There's several parts of this table that we'll
20 go through, but the first part involves the first three
21 entries, these first three compounds here, and the way these
22 R groups are being varied in these first three entries, as
23 you pointed out, or as I pointed out, or maybe we both
24 pointed out, would be these R groups are the substituents,
25 the R3 and R4 on this nitrogen atom. And so if you have as

1 R3 and R4, you have Hs, that compound would be called a
2 primary amine. So there's a categorization of amines based
3 on primary, secondary and tertiary, and that's probably
4 language that's been used already in these proceedings, but
5 if there is -- there are three substituents on the nitrogen,
6 it's tertiary; if there's two substituents, two carbon
7 substituents on the nitrogen, it's secondary; and if there's
8 only one carbon substituent, it's primary. So this first
9 entry has one carbon substituent, both these carbons are Hs
10 and so it's primary, and you can see that when you look at
11 the activity of that compound, essentially, there's no
12 analgesic activities at the maximum dose they looked at.

13 If you look then at the compound where one of
14 these R,S is H and one of them is a methyl group, that's
15 this compound, this compound also seems to be devoid of any
16 analgesic activity.

17 But when -- both of these R groups are methyl
18 groups, CBCH3 groups, and that now we call a dimethylamino
19 group because there's two methyls and an amino group, that
20 compound now has quite nice analgesic activity.

21 Q. Okay. So what they've done is, they've kept
22 everything else the same. This first column is R1. That's
23 the group on the phenyl ring; is that right?

24 A. Right, that's maintained the same. R2 is maintained
25 the same.

1 Q. R2 is this group here on the bridge carbon, what they
2 call the bridge carbon?

3 A. Correct.

4 Q. So they've kept those things the same, and they've
5 varied the nitrogen by either taking one or two methyl
6 groups off and replacing them with hydrogen. Is that what's
7 happened here?

8 A. Well, the way the table is arranged, it looks like
9 it's the opposite, but yes, that's essentially it.
10 Whatever. It's the same thing, yes.

11 Q. Okay. And when they did that, when one methyl group
12 is replaced with hydrogen or when both methyl groups are
13 replaced with hydrogen, the analgesic activity disappears.
14 Does that look like what happened?

15 A. That's correct.

16 Q. And now, L 201 that's listed here, that's the compound
17 with the two methyl groups on nitrogen?

18 A. That's correct.

19 Q. Okay. And you understand that that is tramadol?

20 A. Yes, that has the formula -- structural formula of
21 tramadol.

22 Q. Okay. Does it include the S,S and R,R enantiomers of
23 tramadol?

24 A. It does.

25 Q. Does it also include the S,R and the R,S enantiomers

1 of tramadol? Do you know that from this paper?

2 A. You don't know that from this paper, no. This paper
3 is silent on the presence of diastereomers.

4 Q. Is there any other information that you have in the
5 prior art that might inform you as to what exactly is L 201
6 with respect to whether it's just the two tramadol isomers
7 or also the other two R,S and S,R isomers?

8 A. Yes, the other paper that presents information on this
9 is a paper by Frankus, one of the coinventors of tramadol
10 and also co-author on this paper, and he's studied that, so
11 he's the one -- you know in reading his paper that this
12 L 201 is the mixture you referred to, the so-called R,R,
13 S,S, R,S and S,R.

14 Q. Okay, and we'll look at Frankus in a little bit.

15 Do you know if this L 201 is predominantly more
16 R,R S,S, or R,S S,R?

17 A. I -- I can make a reasonable guess based on the
18 Frankus paper, yes.

19 Q. Okay, and we'll look at that in a bit.

20 I'll just show you on the ELMO, the authors of
21 this paper have summarized just below, just in table -- in a
22 section called 3.2.1 a heading called "Group I,"
23 "Substitution on the amine nitrogen." Do you see that?

24 A. I do.

25 Q. And what are the authors concluding from the data you

1 looked at?

2 A. Well, this actually summarizes more than the data
3 we've discussed, but it's still the same conclusion.

4 Q. Just focus on the data that we just discussed, please.

5 A. It says that "The dimethylamino derivative has the
6 strongest analgesic activity."

7 Q. And then continuing on?

8 A. "This is already lost entirely when one methyl group
9 is replaced by a hydrogen atom. The bis-desmethyl
10 derivative E450 is also inactive as an analgesic."

11 Q. Now, How do you relate this to your opinion regarding
12 the tramadol or minus O-desmethyiltramadol pharmacophore?

13 A. Well, based on what we've analyzed so far, it says
14 that you need -- the dimethylamino group is important, and
15 that based on the information we looked at, it also says
16 that -- well, another way of saying it is that the primary
17 means and secondary means are not good.

18 Q. Okay. And these authors also in the Discussion
19 section, at section 2 of the Discussion section discuss
20 replacement of one or both methyl groups with hydrogen; is
21 that right?

22 A. That's right.

23 Q. And what do they conclude based on this data?

24 A. Well, again, they say "The analgesic activity is
25 associated with the dimethylamino group. The replacement of

1 one or both methyl groups with hydrogen eliminates the
2 activity."

3 Q. Okay. Let's go back to the slide.

4 Okay. And continuing in Table 3 -- well, there's
5 your -- that's the conclusion that you just made?

6 A. Yes.

7 Q. And can you just read that conclusion into the record?

8 A. Oh. I'll read it again. Yes. "Primary and secondary
9 amine derivatives of tramadol are much less active as
10 analgesics."

11 Q. Thank you.

12 And then continuing, here's another highlighted
13 portion that you've made of Table 3.

14 What's the take-home message here? What are the
15 key points here with respect to your opinion?

16 A. Well, basically what's being done here is looking at
17 other groups other than methyl as substituents for R3 and
18 R4, taking less --

19 Q. I'm sorry. We're still keeping R1 and R2 the same?

20 A. R1 and R2 will remain the same

21 Q. And now we're making changes from L 201's two methyl
22 groups. What are we doing now?

23 A. We're changing those to two substituent groups. In
24 the next case down, I can't read that --

25 Q. L 228. Do you see that?

1 A. Yes, L 228, you're replacing them it looks like with
2 ethyl groups, so instead of methyl, this is a two-carbon
3 group called the ethyl group. So you replace both of them,
4 the activity goes away.

5 Q. Sorry. So that's instead of one carbon, now we have
6 two carbons on each nitrogen?

7 A. Right. So we're comparing these all with the sort of
8 parent, L 201.

9 Q. Okay. And each group, rather than being one carbon,
10 one CH₃ methyl group, now each group is C₂H₅.

11 A. That's correct.

12 Q. And what happens to analgesic activity when you make
13 that change?

14 A. It basically looks like it's abolished. It's great,
15 they only measured this up to looks like 200 milligrams per
16 kilogram, and there was no activity.

17 Q. So the highest dose they tested, they could not see
18 analgesic activity; is that right?

19 A. That is correct, that's what it looks like.

20 Q. And the next entry down, L 206, what did they change
21 here?

22 A. Again, the only thing they're changing are these
23 groups on the nitrogen atom, and now they're changing them
24 both. Both of those methyl groups that were up here in
25 L 201 are being changed to groups they call allyl groups,

1 and an allyl group is -- well, it's three carbon atoms, and
2 it has a carbon-carbon double bond in it.

3 Q. Okay, and what happens to activity?

4 A. Again, the activity, basically, it goes away. At the
5 highest dose they tested, there was no activity.

6 Q. Okay, and the last two entries you have highlighted
7 here are L 208 and E 445. What did they do the nitrogen
8 atom substituents and how did that affect analgesic
9 activity?

10 A. Well, again, in this case the first example here,
11 L 208, they changed one of the substituents, one of the
12 methyl groups to a benzyl group, and that benzyl group is an
13 aromatic ring with one carbon atom, and the activity again
14 at the highest dose they tested, there was no analgesic
15 activity. When they made both of these R groups on the
16 nitrogen atom, benzyl groups similarly, there was no
17 activity at the highest dose they tested.

18 Q. Okay. And now let's go to the ELMO for a second.

19 Looking at the English translation of the Flick
20 1978 paper, section 3.2.1, how do the authors of this paper
21 characterize the changes that you just made as they impact
22 analgesic activity?

23 A. So reading from here, and I'll have to go read it on
24 my monitor, it says "Likewise the replacement of the methyl
25 groups by higher homologs such as ethyl (L 228), allyl

1 (L 236) or benzyl groups (L 208, E 445) also leads to
2 disappearance of the analgesic activity."

3 Q. And Professor Martin, if it is easier, you do have the
4 paper copies.

5 A. Oh, yes, I've got -- yes, I don't have that out.

6 Q. Okay.

7 A. And it's easier for me to look here because I have to
8 find it in the other copy.

9 Q. Understood.

10 Okay. And how do you summarize this data?

11 A. Well, basically similarly. I summarize it by saying
12 "replacing the methyl groups, these CH₃ groups with other
13 alkyl groups results in significant loss of...activity."

14 Q. And these authors did one more thing with this group.
15 What's being presented in this table with respect to the
16 things they kept the same and the things that they varied on
17 the nitrogen atom?

18 A. Okay. So once again, they're keeping everything the
19 same except what's on the nitrogen atom, so the R₁ group --
20 the substituent on the aromatic ring and the OH is the same
21 -- there we go -- the OH is the same. And so what we're
22 changing are these R groups on the nitrogen atom. And now
23 these are -- these are cyclic groups, these are rings, so if
24 you see this little sort of space here, the nitrogen atom
25 would be in here, in this particular example the nitrogen

1 atom is in a five-membered ring with four carbon atoms and
2 the nitrogen atom. When you do that, you abolish activity.

3 If you put the nitrogen atom up here so you make
4 it part of the ring, this time the ring contains two carbon
5 atoms -- four carbon atoms, I'm sorry -- totally and an
6 oxygen atom. That also abolishes activity.

7 The nitrogen atom is part of a six-membered ring,
8 so we've got four -- five other carbon atoms and the
9 nitrogen atom, that also abolishes activity.

10 Q. Okay, and when you say they make a ring, looking at
11 the structure, this nitrogen combined with R3 and R4,
12 together, these are all part of a ring; right?

13 A. Correct.

14 Q. And compounds L 218, L 206 and L 225, right?

15 A. That is correct.

16 Q. Okay. And then looking at the ELMO again, in the
17 conclusions of this paper, what did the authors conclude
18 with regard to possibilities for substitution on this
19 nitrogen atom?

20 A. Well, they basically concluded it's extremely limited.
21 They say "In the phenyl cyclohexanols, the substitution
22 possibility on the nitrogen is extremely limited. Among all
23 of the amines investigated, only the dimethylamino group
24 showed analgesic activity."

25 Q. And other than the Flick 1978 paper that we're looking

1 at, are you aware of any other publications dated prior to
2 1994 where this substitution pattern on nitrogen in these
3 compounds, these compounds that include tramadol and other
4 cyclohexanols, are you aware of any other paper that
5 conducted a structure activity relationship study with
6 respect to that group?

7 A. No, I'm not aware of any other studies that looked at
8 that. This is the -- the only one.

9 Q. Okay. Well, let's look at some other things that were
10 varied in the Flick 1978 paper.

11 Here's your conclusion slide on the dimethylamino
12 group, and what is your conclusion with respect to things
13 that are taught in the Flick paper with regard to this
14 substitution?

15 A. Well, these actually are not my conclusions. These
16 are lifted from the paper itself. So these are statements
17 by the authors, by the people who did the work. These are
18 their conclusions. They say "The analgesic activity is
19 associated with the dimethylamino group. The replacement of
20 one or both of the methyl groups with hydrogen eliminates
21 the activity. Substitution with higher alkyl groups or with
22 substituents in which the nitrogen was integrated into a
23 ring system also leads to loss of effect."

24 And then I think we said this before, didn't we,
25 that "In the phenyl cyclohexanols the substitution

1 possibility on the nitrogen is extremely limited. Among all
2 of the amines investigated, only the dimethylamino group
3 showed analgesic activity."

4 Q. Okay, and what do you say at the top?

5 A. Well, yes, so in my -- what's been at the top of all
6 these slides is the fact that this dimethylamino group is
7 important and it should not be changed. It is part of the
8 tramadol pharmacophore.

9 Q. Okay, and I just want to note for the record that
10 Defendants' Exhibit 834 is the English translation of the
11 Flick 1978 paper, although the photocopy quality is not very
12 great.

13 Let's look at some other things that Flick changed
14 in his structure activity relationship study.

15 Now, this is in Table 4 of Flick.

16 Can you tell us, Professor Martin, walk us through
17 what's being varied here, what's being kept the same and how
18 the changes influence analgesic activity?

19 A. Well, this table actually shows a number of things,
20 some different things going on. So let's focus first on
21 what I've got here, and that has to do with the substituent
22 on the bridge carbon, and it's saying it may be changed.
23 Again --

24 Q. I'm sorry. Can you just explain, clarify what you
25 mean by the bridge carbon?

1 A. I was just about to.

2 Q. I'm sorry.

3 A. So the bridge carbon is a term that is used by the
4 authors, and it is --

5 Q. Is it this group that --

6 A. Yes.

7 Q. -- at R2?

8 A. Right, it's at group R2. So the bridge carbon is the
9 carbon to which R2 is attached. It's the same carbon atom
10 that is attached to the phenyl ring, the aromatic ring, and
11 is a carbon in the chain, the three-carbon chain that links
12 the aromatic ring with the dimethylamino group as you're
13 showing on the slide, right.

14 So the question is, is, what can we do, what
15 changes in substitution can we make at that carbon atom and
16 retain biological activity?

17 And so I've highlighted three examples here --
18 three things here, again starting with L 201, and in all of
19 these examples, the substituent on the aromatic ring is the
20 same, it's methoxy, and if you could -- okay, mine's working
21 again. So the methoxy is the same in all of these cases.
22 The dimethylamino group is in all of these cases, so both of
23 these R groups are methyl in all these cases.

24 So those are staying constant, as well as the ring
25 size, and which we'll come to momentarily. The ring size in

1 these three examples is constant.

2 MR. CAPUANO: Your Honor, may I give the witness
3 maybe a better laser pointer?

4 THE COURT: Yes, definitely. Go ahead.

5 MR. CAPUANO: Maybe that will work better.

6 THE WITNESS: Oh, yes. Okay.

7 A. So do you want me to go through --

8 Q. What I'd like you to do is explain the activity
9 chains, going for example from L 201 to E 609.

10 A. Okay. So in that particular chains, we are converting
11 this R group from a hydroxyl group that's here to a hydrogen
12 atom, which is down here. And so the question is what's the
13 effect of doing that.

14 And so you can see over here this is the analgesic
15 activity, which is the biological readout here, analgesic
16 activity for OH, and we'll just focus on these numbers
17 outside the parentheses for the moment, is 16, and I'll
18 round it off, and down here it's 24, it's about, almost 24.

19 Q. Okay.

20 A. So there's a -- the author's described this as a
21 slight loss of activity.

22 If I look at this and consider the -- what's in
23 the brackets here, I see overlapping arrow bars, overlapping
24 results here, so I would say they're comparable, but there's
25 no real loss of activity by making that replacement.

1 Q. Okay, and let's look at what the author said in
2 section 3.2.2.2 of the paper with respect to that compound
3 E 609. Do you see that? It's highlighted here.

4 A. Right. Right here. So E 601, which has a hydrogen
5 substituent on bridge carbon C1, and skipping a little bit,
6 "should have no analgesic activity," because it doesn't
7 correspond to the structure of the morphine analgesic.

8 Q. Let me just interrupt you there. I apologize.

9 What is your understanding of the meaning of this,
10 that with the hydrogen there at the bridge carbon it no
11 longer corresponds to the general formula of the morphine
12 analgesic?

13 A. So I talked about this briefly when we had the Hennies
14 article up.

15 Do we need to get that up again?

16 Essentially, what it's saying is that that bridge
17 carbon and the morphine-related compounds is always fully
18 substituted.

19 Q. And by "fully substituted," do you mean has four
20 nonhydrogen substituents on it?

21 A. Yes, it has four nonhydrogen atoms associated with it.

22 Q. Okay. Please continue.

23 A. Okay. So their thought, I think, when they did this,
24 was that, their prediction was that it should not have any
25 analgesic activity.

1 However, they say, "The prediction was not
2 confirmed for compound E 609. This substance, with an ED50
3 of 23.6 milligrams per kilogram p.o.," which is oral, per
4 os, "has strong analgesic activity."

5 Q. Okay. So going back to the slide, what does this tell
6 you about that group, that bridge carbon group R2? You have
7 here in your statement that it may be changed. At the top.

8 A. Ah. Right. So I'm saying that substituent on the
9 bridge carbon may be changed without significantly change --
10 altering or losing biological activity.

11 Q. Okay. Let's look at the next slide.

12 What are you showing in this slide? This is the
13 same Table 4. You've got a couple different rows
14 highlighted. Can you explain what's being changed here?
15 What is the change that's being made and how does that
16 affect analgesic activity?

17 A. Okay. So, again, the benchmark compound is L 201,
18 where we have the OH, and now the difference between this
19 compound -- again, the ring size is the same, the
20 substituents on the aromatic ring are the same, the
21 substituents on the nitrogen atom are all the same, but what
22 we've done is, we've performed a reaction, and our organic
23 chemist would refer to these compounds as esters of this
24 hydroxy compound.

25 Q. Okay. And can you explain what an ester is and how

1 L 205 and L 204 differ in structure from L 201?

2 A. Right. So what's happened here is that we've replaced
3 this hydrogen on the OH with a -- well, that's what we've
4 done is we've replaced this hydrogen on the OH with this
5 group here, which is a carbon doubly bonded to an oxygen
6 atom with another carbon atom. So that's a functional group
7 in organic chemistry, and that's an ester.

8 Q. And when you make that change, what does the structure
9 activity result -- what does the structure activity resolve
10 with respect to analgesic activity?

11 A. Again, it's -- it's virtually all lost. At the
12 highest dose they looked at, this showed no activity. It
13 looks like this may show some activity at 200 milligrams per
14 kg. So you lose -- you lose biological activity. You lose
15 analgesic activity.

16 Q. So when we looked at the time change to hydrogen, you
17 said that was something that may be changed that shows that
18 the bridge carbon may be changed --

19 A. Yes.

20 Q. -- and here you're saying what, that -- what are you
21 saying here?

22 A. Well, I'm saying we would not change the hydroxyl
23 group to groups like this.

24 Q. Okay. So some changes look like they might be
25 promising and others do not; is that right?

1 A. That's exactly right.

2 Q. Okay. And let's continue. This is Table 5 of Flick.

3 Can you tell us again here, now, what did Flick
4 change and what did those changes mean for analgesic
5 activity, and also, maybe in doing that, could you explain
6 what these little m's and p's are? In the R1 column.

7 Sorry, sir.

8 A. I've highlighted the two compounds that I would say
9 are most referred. One is tramadol, one is the
10 desmethyltramadol.

11 What's not being changed is the nature of the
12 bridge carbon substituent, so that's OH in all cases. The
13 substitution on the nitrogen is not being changed, so that's
14 this dimethylamino group in all cases.

15 And so what's being changed now is this
16 substituent R on the aromatic ring.

17 Q. Okay.

18 A. And it's being changed through a variety of things
19 you can see here.

20 Now, you asked about the m's and the p's.

21 Q. Right, and -- go ahead.

22 A. So this refers to the orientation on the aromatic
23 ring.

24 Maybe I could use the model. I don't know.

25 Q. If you could use the model to help. It will at least

1 give us something to do with our hands.

2 A. Yes. I see people have been playing with it, so
3 hopefully it's still in its proper form.

4 Q. So you have the -- what are you holding there?

5 A. So this, Your Honor, is the model with two rings, and
6 this is the cyclohexane at the bottom. And so this is the
7 aromatic ring. This is the phenyl ring that we've been
8 talking about. So there's one substituent here, and there's
9 another substituent over here.

10 So these two substituents are in a 1-3
11 relationship, and so that's referred to by organic chemists
12 as meta to each other. If they were a 1-2 relationship to
13 each other, we'd call that ortho. We don't have that up
14 here. And with the 1-4 relationship, so a substituent on
15 this carbon atom, not this one, that would be para. These
16 things here with nothing dangling on it are hydrogen atoms.
17 And so --

18 Q. And so when you say one, two, three, four like that,
19 are you counting around the ring?

20 A. I'm counting around the ring from the carbon atom that
21 is bonded to the cyclohexane ring.

22 Q. Okay. So if two things are on adjacent carbons, you'd
23 call that 1-2?

24 A. 1-2, or ortho.

25 Q. And then 1-3 you would call?

1 A. Meta.

2 Q. And that's what m means in this table?

3 A. That's what m means in this table. And as you can
4 see, with two exceptions, R is a meta substituent. The
5 first entry, there's no substituent, it's a hydrogen. And
6 in an entry, I don't know, E 432, it's a paramethoxy group.
7 So that methoxy group is at the 4 position.

8 Q. Okay, and then looking at what you have highlighted,
9 here you've highlighted L 201, which has meta O methyl. Is
10 that right?

11 A. That's correct.

12 Q. And you're comparing that with L 235, which, again, is
13 still meta, still at the same position on the ring, but now
14 instead of O methyl it's O hydrogen; is that right?

15 A. That is correct.

16 Q. And this is the same difference between tramadol and
17 O-desmethyiltramadol; is that correct?

18 A. That is correct.

19 Q. Okay, and when you make that change, when you go from
20 the meta O methyl that's in tramadol to the methyl
21 O hydroxy that's in O-desmethyiltramadol, what happens to
22 analgesic activity?

23 A. Well, it's much greater if you have the hydrogen, the
24 OH. It gives you much better analgesic -- much better.
25 It's about a factor of three here.

1 Q. And then so with this data, does that give you any
2 information about the relative analgesic activity of
3 tramadol versus O-desmethyiltramadol?

4 A. Yes. The tramadol has less analgesic activity.

5 I think another important point to make here also
6 is a column we really haven't talked about yet. So there
7 are a number of biological readouts here. There's a column
8 here I really haven't discussed, which is the toxicity,
9 which is something you don't want. But the other important
10 thing is this therapeutic index. And so this
11 desmethyiltramadol has a threefold better therapeutic index,
12 too, so when you're making compounds for giving to humans,
13 you want to maximize the therapeutic index.

14 Q. Okay. So for that column, therapeutic index, it's
15 actually the higher number that's the more --

16 A. That's correct. It's essentially a ratio of the toxic
17 effects with the beneficial effects.

18 Q. Okay. I'm just looking at what the authors had to say
19 on the ELMO here in the bottom section of 3.2.3. Do you see
20 where it says "substitution on the phenyl ring"?

21 A. I'm sorry, point -- where are you -- oh, right. Oh,
22 okay. "Substitution on the phenyl ring." Yes. Yes, I do.

23 Q. And what does it say about that compound, L 235, that
24 we just looked at?

25 A. Let me read it. I think it says it was maximum.

1 Q. Sorry. Oh, there you go.

2 (The document was redisplayed.)

3 A. So it essentially says "The action maximum is seen
4 with the meta hydroxyl derivative (L235), for which an
5 analgesic ED50 of 5.2 milligrams per kilograms oral was
6 found." So it's saying the meta hydroxy group is the best
7 group.

8 Q. And what does it say about when you make that a methyl
9 group instead for L 201?

10 A. It says "Conversion of the free hydroxyl group to the
11 methyl ether (L 201) weakens the effect to an ED50 value of
12 16.1," and to read further, we didn't talk about these
13 compounds, but extension to the ethyl, ether, L 233 or
14 conversion to the benzyl ether, L 230, causes a further
15 decrease in activity.

16 So of the various substituents on an oxygen atom,
17 alkyl groups, that is, nonhydrogen substituents, again, the
18 methyl group is the best.

19 Q. Okay. Let's go back to the PowerPoint, please.

20 Now, also in this table, you did note the one
21 compound where there's a parasubstituent. Is that E 432?

22 A. That is.

23 Q. Okay, and can you compare E 432 with L 201 and talk
24 about what that change from meta in L 201 to para in E 432
25 means for analgesic activity?

1 A. Yes. There's a dramatic decrease. So I mean, here is
2 the paramethoxy. Everything else, again, is the same. And
3 you can see if you look in the column for analgesic activity
4 that it's about 200, so that's saying that they had to go to
5 a dose of 200 milligrams per kilogram to see much of an
6 effect.

7 Q. Okay. So just moving that group, that OCH3 group from
8 the 3 position to the 4 position does what for analgesic
9 activity?

10 A. Well, it has a dramatic negative effect. There's a
11 big loss in activity. And so that wouldn't be -- that would
12 be something you would not want to do in making analogs
13 because you know from the prior art that that's deleterious.

14 Q. Continuing on, in Table 4, Demonstrative slide 29,
15 what are you trying to explain here, Dr. Martin, with
16 respect to Table 4?

17 A. So these entries that -- we've been at Table 4 before
18 but now I'm focusing on a slightly different change, and so
19 you'll notice that the group on the aromatic ring, this
20 R group, is the same. We're dealing with the same bridge
21 carbon substituent. We have the dimethylamino group here.
22 So the only thing we're changing now is the size of this
23 ring.

24 And so what they did was to see what the effect
25 of constricting the ring is, that is, reducing the ring size

1 from six to five, and they look to see what expanding the
2 size of the ring would do, that is, changing the ring size
3 from six to seven.

4 Q. Okay. So in tramadol or in L 201, that ring has six
5 members; right?

6 A. Yes.

7 Q. And we call that cyclohexane; correct?

8 A. That's correct.

9 Q. And they looked at, for E 601, where N is zero, now
10 that's a five-membered ring, right?

11 A. That's a five-membered ring. That's a cyclopentane.

12 Q. Okay. And then if you go from six and make it bigger
13 to seven, is that what's being done for compound L 257?

14 A. Yes, it is. And so that seven-membered is
15 cycloheptane.

16 Q. Right. And what does the data show when you go from
17 the six-membered ring of L 201 and either make it smaller or
18 bigger by one carbon?

19 A. Well, so if you make it smaller, you see a dramatic
20 loss of analgesic effect, so, again, about 200. When you
21 make it larger by one carbon atom, you lose analgesic
22 activity -- you lose significant analgesic activity.

23 Q. Well, and in particular, what happens to toxicity when
24 you make the ring bigger? How does that -- how is that
25 reflected in the therapeutic index?

1 A. Well, the therapeutic index drops to 5.1. So the
2 analgesic activity dropped by a factor of three. The
3 therapeutic index got less favorable by a factor of five.
4 So it got even worse because of the slight increase in
5 toxicity.

6 Q. Okay. And what do the authors conclude with respect
7 to this data you have here on your slide?

8 A. So again, this is taken directly from the paper
9 itself. "The constriction or expansion of the cyclohexyl
10 radical results in a loss of activity. This is much weaker
11 in the case of ring expansion to cycloheptane than in the
12 case of reduction to a cyclopentane ring."

13 Q. Now, continuing on, tramadol, as we've discussed, as
14 several witnesses have discussed in this trial, is a mixture
15 of R,R and S,S enantiomers, and that's shown here on the
16 slide.

17 A. Shown on the left on this slide, right.

18 Q. Now, is there information in the prior art before 1994
19 on how the stereochemical relationships in these compounds
20 relate to their analgesic activity?

21 A. There is, and this is this paper by Frankus that we
22 alluded to earlier from 1978.

23 Q. I'm sorry. Let me just bring that up.

24 A. Oh.

25 Q. Defendants' Exhibit 717.

1 Do you recognize Defendants' Exhibit 717,
2 Professor Martin?

3 A. Right. This is the German version of the Frankus
4 paper. It's talking about separating the isomers,
5 structural determination, pharmacological effects.

6 Q. Okay. And this paper is in the German language except
7 for the summary; is that right?

8 A. I believe that's correct. Yes, that seems correct.

9 Q. Okay. And you've reviewed an English -- have you
10 reviewed an English translation of this as part of your work
11 in this case?

12 A. Yes, in addition to looking at the German version, I
13 reviewed the English translation.

14 Q. Okay. And let's put up the English translation.

15 MR. CAPUANO: Your Honor, the English version of
16 this document -- Ted, I can use the ELMO if you can't find
17 it -- is a document that was produced in this case. It
18 doesn't appear on anybody's exhibit list, and so I'd like to
19 mark it as Defendants' Exhibit 2052.

20 THE COURT: Any objection to that?

21 MR. BEST: We have no objections, Your Honor.

22 THE COURT: Thank you.

23 (Defense Exhibit DFX 2052 marked for identification)

24 Q. Looking at page two of what's been marked as
25 Defendants' Exhibit 2052, Professor Martin, do you see two

1 structures there on the page?

2 A. I do.

3 Q. Okay, and what are these representing?

4 A. Well, these are representing the two diastereomers of
5 tramadol. They're the cis form and the trans form. And
6 it's the trans form that is the tramadol structure, and so
7 this structure, the cis form is a diastereomer of tramadol,
8 so which means these two compounds are not mirror-image
9 isomers, they are stereoisomers. They differ with respect
10 to the way the atoms are arranged in space, but they're not
11 mirror images isomers, and we call those diastereomers.

12 Q. Is it the case that the two isomers that are in the
13 trans form are the two isomers that are in the mixture of
14 tramadol?

15 A. That is correct.

16 Q. And the then two isomers that are in the cis form,
17 those are not in tramadol; is that right?

18 A. Well, there could be traces of it in tramadol, I
19 suppose, but not that I know of, no.

20 Q. If they were there, they would be there as impurities;
21 is that your understanding?

22 A. They would be there as impurities.

23 Q. And what did Frankus do with respect to looking at the
24 analgesic activity of these different forms of tramadol, the
25 cis and trans forms?

1 A. So this is the table I sort of talked about. So here
2 you see the L 201, and he presents that as a mixture of cis
3 and trans isomers.

4 Q. Actually, the German DTX 717 table, on Exhibit page
5 eight. It's easier to look at. It's DTX 717, Exhibit page
6 eight, Table 6.

7 There you go.

8 So what's being compared here, Dr. Martin?

9 A. Okay. So as I started, we've got the L 201, so this
10 is a mixture of the cis and trans isomers. It doesn't say
11 what the mixture is in this table. It gives an activity.
12 And then what Frankus did was, he separated the two
13 compounds, the two -- the two forms, the trans and the cis.
14 And so we've got the tramadol structure here, and he gives
15 us the analgesic activity of that, and it's 10.3, and then
16 that's the trans isomer, and then the cis isomer is the next
17 entry, it's E 383, and he gives the activity of that
18 compound, again, a mixture of enantiomers, and it 's 78. So
19 it's -- you know, it's about eightfold less potent as an
20 analgesic than tramadol itself.

21 Q. Okay. And what does this tell you with respect to the
22 importance of stereochemistry in tramadol?

23 A. Well, it tells you that the relative stereochemistry
24 in tramadol is important, because if you change the relative
25 stereochemistry at those two centers, in other words, if

1 it's R,S and S,R instead of R,R and S,S, that's bad. That's
2 something you don't want to do because that gives you a
3 significant loss in analgesic activity.

4 MR. CAPUANO: Okay. Let's go back to the
5 PowerPoint.

6 Q. Now, Professor Martin, we've looked at Flick 1978 and
7 Frankus 1978. In your opinion, are those the two most
8 important prior art references for learning about the
9 structure activity relationships for tramadol and other
10 cyclohexanols in that class?

11 A. Yes, they are.

12 Q. Now, you're aware of other references in the prior art
13 that relate to morphine and other opioids, aren't you?

14 A. Yes, there's a lot.

15 Q. Okay. So why is Flick and Frankus more important for
16 a person of ordinary skill in the art looking at the
17 structure activity for tramadol than other papers and books
18 related to opioids more generally?

19 A. Well, I think the important thing is trying to keep,
20 maintain the close structural relationship when you're
21 comparing things for a structure activity relationship. But
22 I said very early on that we would only change one thing at
23 a time, and then we would -- we would move slowly as an
24 iterative process. If we try to compare tramadol and
25 structure activity relationships with tramadol and those

1 with morphine, we're changing a whole bunch of things.
2 We've seen the structures of morphine again in the Hennies
3 paper. They're very, very different. And so there's no
4 expectation that an SAR that's been developed for morphine
5 will be valid for tramadol, and vice versa.

6 Q. And now based on Flick and Frankus, what you referred
7 to as the closest prior art with respect to the structure
8 activity relationships of tramadol, have you summarized your
9 conclusions with respect to those studies?

10 A. Yes. They're outlined on this slide. And so we have
11 the conclusions I have drawn from Flick, and the conclusions
12 from Frankus. And from Flick, I say the analog activity is
13 associated with the dimethylamino group. That's something
14 Flick also -- that's what Flick says.

15 The meta hydroxyl group gives the best
16 strengthening of action. That's a direct quote from Flick.

17 The six-membered ring is better than the five or
18 seven-membered ring. I don't know if that's a direct quote,
19 but that's basically what Flick says.

20 And then finally, the hydroxyl group on the bridge
21 carbon in the 1-position on the cyclohexane ring can be
22 replaced with a hydrogen atom to get a compound which has
23 strong analgesic activity. So that's paraphrased from
24 Flick.

25 And then on Frankus, what we learn is the trans

1 isomer is more active than the cis, and that teaches us that
2 the relative stereochemistry at those two stereocenters in
3 tramadol is important, so they should not be changed.

4 Q. Okay, and based on these structural activity lessons
5 from Flick and Frankus in 1978, those 1978 papers, can you
6 identify or could a person of ordinary skill in the art at
7 the time, in 1994, could that person have identified the
8 pharmacophore for tramadol?

9 A. Yes, and they would have come up with the
10 representation like this, where I've highlighted in red what
11 we've learned, basically, from the prior art of what the
12 important structural features are of tramadol for biological
13 activity.

14 I'm exemplifying this just for R,R tramadol just
15 to simplify the slide rather than to draw four different
16 structures and highlight them the same way. This
17 pharmacophore applies equally to the S,S isomer. It applies
18 equally to the two enantiomers of desmethyldramadol as well.
19 So the regions here in red are those regions that you do not
20 want to change.

21 Q. And that's what you have written here, you have red,
22 known as part of tramadol pharmacophore: "Do not change."
23 Is that what you have there?

24 A. Yes.

25 Q. And let's talk about the green. What do you mean by

1 showing these other parts of the tramadol structure in
2 green?

3 A. Well, okay. So let's start with the easy one. It's
4 the methyl group that's the metabolite. So we know we can
5 change that. In fact, we know if it's H, it's better.

6 The bridge carbon substituent, this hydroxyl
7 group, we know we can change that, to an H, for example.

8 With the cyclohexane ring, we actually don't know
9 very much from the prior art about what we can do with that.
10 What we know is you shouldn't expand the ring size or
11 decrease the ring size.

12 Q. And when you say the prior art, you mean from Flick
13 and Frankus.

14 A. I mean -- no --

15 Q. From Flick.

16 A. In that particular case, I mean Flick. Only Flick.

17 Q. Okay. So part of your three-step analysis, first, you
18 said identify a lead, that's what a person of skill in the
19 art would do, and then that person of skill in the art would
20 identify the pharmacophore, and then what's your third step?

21 A. So then it's time to modify the lead, to try to find
22 the compound with improved analgesic activity. And so what
23 a person of ordinary skill would do was, he'd take these
24 teachings that we've developed, take the prior art teaching
25 and begin to make structural changes and see what the effect

1 of making those structural changes is on the biological
2 activity of the new compound that you make.

3 Q. Okay. And you identified those areas of the molecule
4 in green that were promising or could be promising or at
5 least available for change without interfering with the
6 pharmacophore; is that right?

7 A. That's correct. And so that's where you would start,
8 in my opinion.

9 Q. Okay. And so one of the things you identified was the
10 bridge carbon region. You said that was in green, and that
11 you could change that; right?

12 A. Right. And with the teaching of Flick, we know we can
13 change that to a hydrogen.

14 Q. Okay. Now, you can change it to other things as well,
15 couldn't you?

16 A. You could. The only other substituent -- we didn't
17 discuss it -- the only other substituent that Flick put
18 there and had good activity was the chlorine atom.

19 Q. Okay. And so why would -- you say replace OH with H
20 from Flick. Why would a person of skill in the art be
21 motivated to make that particular change?

22 A. Well, because we're simplifying the molecule. Again,
23 this is, if you will, it's in keeping with the morphine
24 story, the opioid story, we're simplifying the molecule, so
25 we're going to take that group off, and we know we can

1 replace it with the hydrogen and maintain activity. So
2 Flick has already done that for us.

3 Q. And when Flick did that, did he expect there to be
4 analgesic activity when making that change?

5 A. No, I think we discussed that they were a little
6 surprised at that because it was a departure in their view
7 from the morphine -- the opioid analgesics.

8 Q. Okay. And what would a person of ordinary skill in
9 the art make of that change from OH to H, which was expected
10 by the authors not to have activity but, in fact, resulted
11 in what they called strong activity?

12 A. Well, you know, I think that would catch the person of
13 ordinary skill's -- the person of ordinary skill in the art,
14 that would catch his or her attention, and so that would be
15 an interesting place to start.

16 Q. And then one of the other areas -- and there's that
17 change shown on the slide from OH to H.

18 The other area you said could be promising for
19 modification or at least wouldn't interfere with the
20 pharmacophore, which we know we can't change, was the
21 cyclohexane region. And what are you showing here on this
22 slide?

23 A. So I'm showing three different possibilities for how
24 you could modify the cyclohexane ring.

25 Q. Okay. Take us through each of those.

1 A. Okay.

2 Over here on the left-hand side of the slide, I
3 referred to this as the open ring, so we're going to open up
4 the cyclohexane ring, and I refer to this as a scission
5 mode.

6 The second box here describes another way to open
7 the cyclohexane ring where you would remove carbon atoms,
8 and I have highlighted the carbons 1 and 2 here as those you
9 would remove.

10 You notice I have bonds A, B and C and I have only
11 carbons 1 and 2, and you might ask, well, why not cleave
12 other bonds? Why not remove other methylene groups or
13 carbon atoms?

14 And the answer to that question very clearly is,
15 if you do that, you destroy these stereocenters, you remove
16 these stereocenters and you lose what we'll learn and what a
17 person of skill would have known are important control
18 elements for maintaining the three-dimensional shape of
19 these molecules in a way that corresponds to the
20 six-membered ring compounds.

21 Q. Okay. So we're not going to touch the red part;
22 right? That's the pharmacophore.

23 A. We're not touching the red.

24 Q. And in your open-ring version called scission, what
25 you're suggesting is you just cleave one of these bonds, A,

1 B, or C. Is that the structure you're suggesting?

2 A. That's what I'm suggesting.

3 Q. And when you would do that, you would form an
4 open=ring structure; is that right?

5 A. You would form an open ring, an acyclic molecule, I
6 think it's been referred to as a linear compound in these
7 proceedings.

8 Q. Do you remember Dr. Buschmann calling it linear?

9 A. Right. Right.

10 Q. Okay. And then so in your second option for opening
11 the ring, you say you could just remove or excise a carbon.
12 Is that what you're showing there?

13 A. Right. You could excise either one of these or both
14 of them.

15 Q. Okay. But you couldn't excise any of the red ones;
16 right?

17 A. No, because, again, if you did that, you would remove
18 the stereocenter here, and as I'll try to explain, it's not
19 going to be easy, but as I'll try to explain, you would lose
20 the conformational preferences about this carbon-carbon bond
21 that are very important in terms of maintaining the
22 three-dimensional aspects of the pharmacophore.

23 Q. And does Flick give you any information on making the
24 ring bigger or smaller? We looked at that; right?

25 A. Right. He doesn't give us -- no guidance on anything

1 else. No guidance on substitution, either.

2 Q. And the third option you have is what you call
3 substitution, and what's that? That's when you start adding
4 things --

5 A. Right.

6 Q. -- or changing the ring?

7 A. Right. So these R groups could be added at a number
8 of positions. You'd have to be careful, again, because
9 adding those R groups at certain places might have adverse
10 effects on the conformational preferences, but you could
11 analyze that and predict what those might be.

12 That, you know, that kind of flies in the face of
13 the strategies in the art for making opioid, improved opioid
14 analgesics. In this case, we're actually adding
15 complexities. If I start adding substituents back to the
16 compound, I'm making the structure more complicated, not
17 simpler.

18 Q. So this option, the substitution option that you've
19 put here, although theoretically possible, is it the case
20 that it would go against the -- what, the way these
21 compounds have been -- well, explain. How would
22 substitution be something that would or wouldn't be looked
23 at as favorable for a person of ordinary skill in the art?

24 A. Well, I don't know favorable or unfavorable. It's
25 just that it's increasing the complexity of the system, and

1 it's increasing certainly the conformational, the
2 three-dimensional complexity of the system and what the
3 results of those substitutions is going to be. So there
4 would be a lot to analyze in those situations, and as I
5 said, I think we started with the work of Hennies and
6 described how in the morphine area we constantly are
7 simplifying things.

8 Q. Okay. And we also know --

9 A. But I can't say it's really bad. It's just something
10 I wouldn't do first.

11 Q. Fair enough.

12 And is the prior art that would guide us in
13 considering options for modifying the cyclohexane ring
14 beyond what -- beyond, say, Flick or the things that were
15 specifically done in that paper?

16 A. Well, so, again, it has to do with adding flexibility
17 to opioids, and I think I pointed out very early on in this
18 it's reiterated in Flick. I mean, Flick basically
19 acknowledges or notes that these compounds that he's made --
20 and these are the compounds in Flick, these
21 phenyl-substituted cyclohexanols, he says, these, quote,
22 "can also be envisioned as highly simplified morphine
23 derivatives the structure of which was made very flexible by
24 elimination of some parts of the ring." And earlier, when
25 we had Hennies up, we showed how that happened, but you can

1 see it here, too. Morphine in a different form, but you can
2 see how much simpler this is. The relationships, again, you
3 can see the two aromatic rings, the six-membered ring here,
4 the six-membered ring here, you can see these relationships,
5 and you can see how this is very much a simplified version
6 of morphine. Morphine is essentially a rigid rock, and
7 tramadol has a number of bonds that you can rotate very
8 easily about, so it's much more flexible.

9 Q. And this idea of flexibility and rigidity, how does
10 flexibility relate to the option of opening the cyclohexane
11 ring?

12 A. Well, when you open the ring, it will be more
13 flexible, and if we go back, if we come back to thinking
14 about what we're trying to do here, I'll come back to this
15 dual mode of action, what is this dual mode of action, it's
16 opioid and it's norepinephrine. And so what we do if we
17 want to optimize the interactions at both receptors is we
18 think about what these molecules are, and if you consider
19 norepinephrine, this is very flexible. There's this ring
20 here, but that phenyl ring is everywhere.

21 This molecule is quite flexible. There's lots of
22 rotational freedom.

23 There are analogs of norepinephrine in the
24 literature. This is an analog that I had in my expert
25 report. It's an analog of norepinephrine. It's a

1 norepinephrine reuptake inhibitor.

2 Duloxetine is a compound that Professor Roush had
3 I think in his opening report.

4 Both of these are compounds are not drugs. They
5 weren't at the time, they were in clinical trials.

6 But these compounds also are very flexible, and so
7 what you'd like to do if you wanted to optimize the chances
8 for enhancing your binding to the norepinephrine receptor,
9 you would say, oh, maybe I should make it a little bit more
10 flexible so it can optimize interactions not only with that,
11 but maybe also opioid receptor.

12 And so we're trying to see if we can make a
13 molecule that -- that fits those receptors a little bit
14 better, and it can do that because it's a little more
15 flexible.

16 Q. Okay, and that increased flexibility, how does that
17 relate to when you want a molecule to be a target for more
18 than one receptor?

19 A. Well, again, more flexible molecules typically are --
20 have -- are a little less selective. They bind to more
21 places, and that can become a downfall for flexibility as
22 well.

23 Q. So, for example, you said morphine, you called it a
24 rigid rock.

25 A. Right.

1 Q. Were you referring to its rigidity versus flexibility?

2 A. Yes, it's rigid. I mean, when you make one of these
3 models of it, it's -- you can't move much.

4 Q. And it's almost, in fact, designed by nature to fit
5 into the opioid receptor; is that right?

6 A. Oh, I don't know what nature was thinking.

7 Q. All right. But it does --

8 A. It happens -- it happens to fit that. But morphine
9 looks nothing like the enkephalins, really, either.

10 Q. And does morphine bind to norepinephrine receptors?

11 Have you seen anything about that in your review?

12 A. No, I don't know anything about that.

13 Q. Okay.

14 So you've talked about how the substitution option
15 -- okay. You talked about how we had the three options, and
16 the substitution option, you said although something you
17 could do, it wouldn't be one of the first things you'd try.
18 Is that --

19 A. I'm sorry, which one? I lost you.

20 Q. Substitution.

21 A. Right. Right. Sorry.

22 Q. Okay, and the other option was scission, and we'll
23 come back to that at the end of the presentation.

24 But here, what you have is this option of what you
25 call excision, removing one of these two, or both, you say,

1 carbon atoms.

2 A. That's correct.

3 Q. Okay.

4 And is the prior art -- well, let me hand you or
5 let me show you Defendants' Exhibit 729.

6 Do you recognize Defendants' Exhibit 729,
7 Professor Martin, and what is it?

8 A. I do. It's a paper by Arbuzov and coworkers. It was
9 published, I think, in 1995.

10 MR. CAPUANO: Show the second page, Ted.

11 A. There must be a page number somewhere. I think this
12 was published in 1955, and it's an account of their efforts
13 to make compounds that have anesthetic activity, and the
14 class of compounds that they were looking at are these
15 1-phenyl-1 alkyl-3-dialkylaminopropanols of that structure.

16 MR. CAPUANO: All right. Let's look at the next
17 page, Ted, and look at what those compounds look like.

18 Q. Where are these compounds, Dr. Martin?

19 A. Okay. So the compounds of interest here would include
20 this group of compounds, and this group of compounds.

21 Q. Okay.

22 A. Is that right?

23 Actually, those two are the same, right? So this
24 one.

25 Q. Okay. And are these compounds related to what would

1 be a ring-open or linear version of tramadol?

2 A. Yes, they are. It's -- it may be a little hard to see
3 it here, and that's why I redrew it on I think the slide you
4 showed a moment ago.

5 MR. CAPUANO: Show the slide.

6 A. Right. So this is the same compound drawn in a way
7 that shows the relationships between this compound and
8 tramadol. I think actually I showed that on the next slide.

9 The point of looking at this, and again, I've
10 tried to emphasize all the way through that one of skill in
11 the art is constantly relying on the available precedent,
12 the prior art, what is known in the literature. And so
13 whenever we have questions of what we want to do as
14 scientists, we ask what's known, and then we make a decision
15 as to, do we follow what's known or do we depart from what's
16 known.

17 And so I think in taking initial steps to develop
18 SAR here, I think what one of skill in the art would do was
19 look for compounds that are similar to the things I have and
20 have to think about, and ask, are they known, and if they
21 are known, is anything known about their activity, and in
22 this particular case, we're interested in CNS, in analgesic
23 activity. And so when you search for compounds, so what a
24 person would do would be to look at this structure, and I've
25 highlighted only one of the carbon atoms, which is the one

1 that corresponds to getting this structure, but remember
2 I've highlighted this carbon atom and this carbon atom over
3 here, but what the prior art tells us is that there is
4 precedent in the literature for taking this carbon out, and
5 that the resultant compounds that you get by doing that
6 operation have CNS activity.

7 So analgesia is a CNS-active thing, and so you
8 would say, wow, that's great, that means I would -- I could
9 do this, I could take this carbon atom out of this molecule,
10 that would give me this molecule, and I would have a
11 reasonable expectation that I would have a molecule that had
12 analgesic activity.

13 Q. Okay. And aside from the Nazarov paper --

14 MR. CAPUANO: Let's put up, Ted, Exhibit 739.

15 Q. Professor Martin, do you recognize Defendants' Exhibit
16 739?

17 A. Right. That's a paper by Spassov, published in 1981.

18 Q. Okay. And -- go ahead, sorry.

19 A. And it's a paper whose focus is on the stereochemistry
20 of these compounds, these diastereomeric
21 3-alkylaminopropanols and their O derivatives.

22 Q. Let's look at the compounds just below that on the
23 first page that are described in the Spassov paper.

24 A. I think 2a is the one that is the close one. So this
25 one here.

1 Q. Okay, is this another linear or open-chain type of
2 molecule?

3 A. It is. And there are two of them here. You see this
4 R group here is either an H or an ethyl, so ethyl is the one
5 that's the close corresponder with tramadol. And also to
6 the point of being closely related to tramadol, you see this
7 -- this amino group here, it has two substituents, and this
8 compound 2a has the dimethylamino group that we learned from
9 Flick is so important in the analgesic activity of compounds
10 of this type.

11 Q. Okay.

12 A. And so 2a is the compound that's a close
13 correspondent. And this compound is identical to the first
14 compound that you highlighted in the Nazarov paper.

15 MR. CAPUANO: Okay. And let's look at the second
16 page of 739, Ted, near the bottom, last paragraph, beginning
17 "The neural pharmacological screening of amine alcohols 1
18 and 2." Just highlight that first sentence.

19 Q. Professor Martin, what activity is described for these
20 compounds in the Spassov paper, Defendants' Exhibit 739?

21 A. Well, again, it talks about these compounds as having
22 central nerve activity, so that's activity in the central
23 nervous system, and in the course of this, you learn that
24 the so-called threo isomers have the greater activity.
25 There's a footnote nine here that relates to the testing of

1 these compounds. There's no information in this particular
2 paper about -- other than the statement about the activity.
3 But it does say the three isomers are the more active.

4 Q. Okay. And the Nazarov and Spassov papers and the sort
5 of open-chain or linear compounds that are described there
6 and their activity, how would those papers inform a person
7 of ordinary skill in the art's decision regarding options
8 for opening that ring and making linear compounds of
9 tramadol?

10 A. As I think I said, if we -- can we go back to the
11 structure --

12 Q. Sure.

13 A. -- maybe the --

14 Q. Here?

15 A. Yes, okay, this structure -- this prior art informs
16 the person of ordinary skill that if you have a compound
17 like this, and you already have the idea, so the person of
18 skill already has the idea, I want to make this more
19 flexible, and I'm looking for how to do that, what are the
20 guides out there to tell me, give me some help on which of
21 these things I should look at first, what should be my
22 priority, because I already know there are a number of ways
23 I can do this. Is there anything that helps me out here?

24 And so the answer is yes, it tells you that this
25 is the carbon atom that you should take out that will give

1 you a compound of this structure, and you can see the
2 relationships once again. The difference is this compound
3 doesn't have the ortho methoxy, and this compound is a
4 mixture of stereoisomers, this one isn't. But we know the
5 importance of this ortho methoxy already, so that's pretty
6 easy to deal with.

7 And so you would have, the person of ordinary
8 skill when they did this would have a reasonable expectation
9 this compound would have analgesic activity. These
10 compounds have CNS activity. And so -- we know this
11 compound does, and so we can expect this compound to have
12 that same activity.

13 Q. Okay, and have you prior to the summary of those
14 modifications to tramadol, O-desmethyiltramadol,
15 modifications that are not part of interfering with the
16 pharmacophore that would be motivated by the prior art?

17 A. Yes, I have two slides here that are very closely
18 related, and they're essentially illustrative of the
19 concepts that we've been talking about. And so we can apply
20 this analysis to the racemate. We can apply this analysis
21 to the single enantiomers. The point is is that here we
22 have tramadol, and -- let's just take this compound over
23 here, we'll just follow it easily, so this happens to be
24 R,R. If we apply the teachings of Flick, we would remove
25 this hydroxyl group, and Flick already tells us at least the

1 combination of these two molecules, I'm going to have
2 analgesic activity. So I already know these have activity.
3 There's no presumption on my part; I know it.

4 And so then we go to the next step and we apply
5 Nazarov, and we do this excision of this carbon, and now
6 from the teachings of Nazarov, I know those compounds have
7 analgesic activity, I would have a very good expectation
8 that these compounds, too, would have analgesic activity.

9 We can turn it around and say, okay, I'm going to
10 apply Nazarov first and get the open-chain compounds and
11 then apply Flick and that takes us to the same point.

12 And these compounds all have the O methyl group.
13 At any point in time here, you could take that methyl group
14 off. But to illustrate them without the methyl group, on
15 the next slide, I do the same thing, and so the explanation
16 is the same: You first apply the teaching of Flick, you
17 apply the teaching of Nazarov, and you're here. Or you
18 apply the teach of Nazarov first, gives you a different set
19 of compounds to test, then you apply the teaching of Flick,
20 and then you're here, you're at tapentadol.

21 Q. And now with respect to making those same changes with
22 what you earlier described as the most promising lead --

23 A. Right, so if we start with the most promising lead,
24 which is minus O-desmethyl, we apply the teaching of Flick,
25 we get this compound, which we don't know anything about,

1 but we then do this, we get tapentadol. We apply the
2 teaching of Nazarov, we get to here, and when we apply the
3 teaching of Flick, we go to here. And so in two steps, we
4 go from the metabolite to tapentadol from our preferred lead
5 compound.

6 Q. Now, Professor Martin, you mentioned you read the
7 transcript of Dr. Buschmann's testimony in court last week;
8 right?

9 A. Yes.

10 Q. And did you read where he testified about how the
11 cyclohexane ring in tramadol was important to obtain the
12 correct positioning of the groups in tapentadol and -- I'm
13 sorry. Let me start it over.

14 Did you read in the testimony of Dr. Buschmann
15 where he testified about how the cyclohexane ring was
16 important in tramadol and O-desmethyiltramadol to obtain the
17 correct positioning of the groups with respect to each
18 other?

19 A. I remember that testimony, yes.

20 Q. Okay. And would a person of ordinary skill in the art
21 have believed in 1994 that the only way to get those groups
22 to adopt that preferred orientation was by maintaining them
23 with the cyclohexane ring?

24 A. No, I would say not.

25 Q. Okay.

1 A. And I -- we have --

2 Q. So can you tell us -- let me just -- this is what
3 we've just been talking about, right? This is tramadol or
4 O-desmethyltramadol on the left?

5 A. Actually --

6 Q. I'm sorry.

7 A. -- this is without the -- the hydroxyl group here.

8 Q. Okay. And Dr. Buschmann testified about a preferred
9 orientation that existed in these compounds based on the
10 cyclohexane ring. Do you remember reading about that?

11 A. Yes.

12 Q. Okay. Now, you've got some funny circles here and
13 some sticks, and we're going to need some explanation for
14 the Court about what these sticks and circles all are about.
15 And have you prepared a way to do that?

16 A. Yes, I have. And let me just first start off by
17 saying that these representations are representations that
18 we call Newman projections. These are -- this is something
19 that we teach in the first semester of sophomore organic
20 chemistry. Everybody that takes organic chemistry learns
21 about Newman projections and how to create them and so
22 forth.

23 And what a Newman projection is, and I have a
24 movie here to kind of help the Court understand this a
25 little bit better, is, what one does is one views down in

1 this particular instance, you view down this carbon-carbon
2 bond. So if you've never seen structures like this, you're
3 probably not going to be able to view down this bond and
4 come up with this. So I'll help show you how we can do
5 that. But -- so the video that we have shows you -- okay.
6 So here's a very simple organic molecule --

7 Q. Let me just -- you might at some point hand out the
8 models with respect to this.

9 A. Everybody has their models?

10 THE COURT: Yes, we do.

11 A. So if you hold the model in front of you like it
12 appears on the screen, -- let me see yours.

13 Has yours been twisted around? Yes. Somebody's
14 been playing with your model.

15 (Laughter)

16 THE WITNESS: Let me fix it for you. Yes. Okay.
17 That's much better.

18 THE COURT: Thank you.

19 THE WITNESS: Small kids like these things.

20 THE COURT: Small kids, adults, everyone.

21 (Laughter)

22 FROM THE GALLERY: Not everyone.

23 (Laughter)

24 THE COURT: Okay. Fair enough.

25 A. So if you hold it, and this is again why we've gotten

1 this model, is two carbon atoms, and these balls, these
2 colored balls are going to represent substituent groups.
3 These two things with nothing at the end, with no balls,
4 these are hydrogen atoms.

5 And so this is the starting structure, and what
6 you're going to see is this structure move, rotate in space,
7 and turn around and be something that you can look straight
8 down that bond. So what you can do is look straight down
9 there, and you can see that arrangement.

10 THE COURT: Okay.

11 THE WITNESS: So if you watch the movie --

12 Q. So is it going to be that you're going to end up
13 looking -- okay. So when this turns, our eyes are going to
14 be looking this way?

15 A. Yes. Right. So it's going to turn, so at the end,
16 what you're going to be doing is looking at it this way.

17 THE COURT: Oh, like this?

18 THE WITNESS: Like this.

19 THE COURT: Looking from this direction?

20 THE WITNESS: Yes, exactly right.

21 THE COURT: Okay.

22 THE WITNESS: Okay. So watch.

23 Q. Okay. Now we're looking down that bond; is that
24 right?

25 A. Right. So now it's like you're looking right down

1 that bond.

2 THE COURT: Okay.

3 A. And if you put this right in front of your eye like
4 this and look straight on to this little black dot, and it's
5 a carbon atom, and put that black dot behind it, you'll see
6 something that very much looks like what's on the screen
7 there. Do you see that?

8 Q. The blue on the upper right, the yellow on the upper
9 left?

10 A. Right. The other direction -- you need to look at it
11 from the other direction. And flip it -- put it like this.

12 Q. The blue should be close to you and the yellow --

13 THE COURT: The blue and the yellow should be
14 close to me.

15 THE WITNESS: Yes, and on top.

16 THE COURT: And on top. I think that's what I
17 have.

18 Now I have it.

19 (Laughter)

20 THE WITNESS: Okay. Now we've got it. It gets
21 more fun as we go.

22 THE COURT: Okay. Keep going.

23 Q. So we're looking down that bond, and now what do we
24 see, Professor Martin?

25 A. Let's leave the blue -- okay. So now what I've done

1 here is brought back that Newman projection from a previous
2 slide so the -- this carbon atom --

3 Q. Maybe I can point.

4 A. This battery is about to die. It was so good for a
5 while.

6 Yes, you're pointing at it. That carbon atom is
7 in the front, and we can't see this atom in the back because
8 we're looking straight down, and what we do is, we represent
9 the carbon atom in the back with this big circle. So if you
10 look at the front carbon atom, you see the yellow ball up in
11 the upper left, the blue ball on the upper right, so you
12 look at the screen, and then you see the red ball, the lower
13 right, and the white ball, the lower left. And the
14 correspondence to this Newman projection that we showed
15 before, if we take away these colors, we see what that looks
16 like, and then maybe if we can go back to the slide that --
17 where we started here -- or maybe we go forward; I can't
18 remember. So basically, now what we have is -- yes, we need
19 a new battery.

20 We have this structure here, which is the --

21 MR. CAPUANO: May I, Your Honor?

22 THE COURT: Certainly. Go right ahead.

23 Q. Here you go.

24 A. Too many people pointing these things.

25 Okay. This isn't as cool as the green one, but

1 here's that structure again, and so if you look at this and
2 then if you sort of fast-forward to the other thing, you can
3 see that they're the same. I don't know if we have to --
4 yes, there we go.

5 So that is the -- and then we'll get to some more
6 of this in a minute. That's the preferred conformation for
7 this molecule.

8 And the important thing to know is that it
9 correlates very nicely with the preferred conformation of
10 this cyclohexane precursor. So this is a little bit more
11 complicated. There are two Newman projections here, but
12 this is a representation of a Newman projection of this
13 cyclohexane, and it's very much the same. We're looking
14 down this carbon-carbon bond. That would be that
15 carbon-carbon bond. And you can see, anyway, that this part
16 looks exactly like this. And in fact, if I were to take
17 away the red lines, this H, the red line and that little red
18 line there, this would look very much like this, and I'd
19 have to take away that little circle back there, but that
20 circle is this carbon atom here. So essentially, these are
21 identical.

22 Q. Okay and so Dr. Bushmann's point is the only way to
23 get this one on the right -- on the left, sorry, is with the
24 cyclohexane ring. Is that your understanding of his
25 testimony?

1 A. That's my understanding of his testimony.

2 Q. Okay, and now on the right-hand side with the linear
3 or open chain, is it the same relative orientation between
4 the nitrogen and the aromatic ring as on -- in the
5 cyclohexane version?

6 A. Yes, it is. You can see it's identical. You could --
7 in your mind, you could pick this up and move it over here,
8 and they would -- you wouldn't see them both, you'd see only
9 one. And we'll do a superimposition later, but we're not
10 ready for that.

11 Q. Now, those models that you have you can spin around;
12 right, Dr. Martin?

13 A. Right. So this is where it gets fun.

14 Q. And when you spin those around, for example, you could
15 spin this around so the nitrogen was on the bottom, right,
16 the nitrogen group?

17 A. Right.

18 Q. Keep going close clockwise until it's over there.

19 A. That's exactly right. You can -- yes, okay. So we
20 don't want -- yes, that's right. That's what we want.
21 Okay.

22 So what Mr. Capuano is saying is, this is the
23 starting point that we just talked about.

24 Let me just explain something here.

25 These two things that you see, if you look down,

1 right down there, you see that these atoms are kind of
2 close, and in reality, these substituent groups are bigger.
3 Well, imagine these as being actually much bigger. I have
4 these little balls, but I don't want to take the Court's
5 time. If you want, I can show you this afterwards, but
6 these --

7 THE COURT: Do it now. You can do it.

8 Q. We can do it now, Professor Martin. It's okay.

9 A. Okay.

10 MR. CAPUANO: We could take a break and he can put
11 it together.

12 THE COURT: That's fine. How much are we
13 thinking, because I'm trying to get a feel for the end of
14 this day.

15 MR. CAPUANO: Getting pretty close to the end. I
16 mean, I've got no more than another 30 minutes.

17 (Off the record discussion)

18 THE COURT: I think we may be very much done for
19 the day. Our Court Reporter has been sitting, and -- I
20 think that that might be it. So you know what? Why don't
21 we do this.

22 (Off the record discussion)

23 THE COURT: You would start again tomorrow
24 morning.

25 MR. CAPUANO: I think I've got a little bit more,

1 and I certainly want to respect the Court Reporter --

2 THE COURT: He's been sitting all day. And I'm
3 grateful.

4 MR. CAPUANO: We can stop.

5 THE COURT: And pick back up with the models in
6 the morning.

7 You know what? Let's do this. Do you want to end
8 at this point? Do you want to ask a follow-up question
9 instead of just taking a break, maybe we could just disband
10 for the day? How would you like to handle it?

11 MR. CAPUANO: I think he's got to put it together.
12 I think it's going to be more than one or two questions.
13 Maybe it's best just to call it a day and continue tomorrow.

14 THE COURT: That's fine. All right. So we will
15 conclude for the day.

16 Yes? Anything?

17 MR. FITZPATRICK: Your Honor, may I raise just a
18 kind of general scheduling issue --

19 THE COURT: Yes.

20 MR. FITZPATRICK: -- for tomorrow and Friday?

21 THE COURT: Yes. What are you thinking?

22 MR. FITZPATRICK: So the Defendants plan to call
23 -- after Dr. Martin concludes tomorrow, our plan is to call
24 three further witnesses this week: Dr. Wolf, Dr.
25 Hollingsworth, and Dr. Prisinzano.

1 We have a fourth further witness, Dr. Buvanendran,
2 who due to professional obligations is not available until
3 Monday.

4 As I understand it from the Plaintiffs, they would
5 prefer to start their rebuttal validity case on Monday also.
6 They wouldn't have witnesses ready to go on Friday.

7 So what we are potentially looking at is perhaps a
8 shortish day on Friday.

9 THE COURT: Which sounds fine, obviously.

10 (Laughter)

11 MR. FITZPATRICK: It's conceivable, although
12 probably unlikely, but it is conceivable that we could, if
13 we had a day like last Friday, for instance, tomorrow, we
14 might not have anybody on Friday.

15 THE COURT: So you're saying if we have a long day
16 tomorrow, we might obviate the need for Friday.

17 MR. FITZPATRICK: It's possible.

18 THE COURT: All right. Well, you know what? Why
19 don't we take it as it is? We'll see how it goes. We'll
20 obviously be able to adjust the schedule. Generally that
21 sounds fine.

22 So what that means, since you're saying we
23 probably would like to sit a long day tomorrow, do you want
24 to start at what time, 8:30 or nine?

25 MR. FITZPATRICK: Nine.

1 THE COURT: Nine? Nine is the preference? Okay.
2 Nine is good? All right. So we'll start tomorrow morning
3 at nine o'clock, and it looks like if we get everything
4 done, we might not have to do Friday. If it looks like we
5 have to do Friday, that's fine, but that would be a short
6 day. Okay. It's going to be a little truncated, which is
7 entirely fine.

8 Let me see. Any other issues before we conclude
9 for the day? Anything?

10 MR. GALLAGHER: Nothing from Roxane.

11 THE COURT: All right. Excellent. Anything else?

12 MR. RICHTER: Nothing.

13 MR. BEST: Nothing from us, Your Honor.

14 THE COURT: All right. So I'll remind the witness
15 that you are still under oath, so you're going to come back
16 and you're going to continue with your testimony. You are
17 not to talk with your counsel about the testimony today and
18 any proposed testimony. All right?

19 THE WITNESS: Okay.

20 THE COURT: Thank you very much.

21 With that, I'm going to adjourn for the day.

22 Thank you, everyone. Thank you very much.

23 THE COURT CLERK: All rise.

24 (Matter adjourned until Thursday, March 17, 2016,
25 commencing at 9 a.m.)

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